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SYNDROME OF RUDIMENTARY OVARIES WITH ESTROGENIC INSUFFICIENCY AND INCREASE IN GONADOTROPINS

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FOR MANY years it seemed reasonable, when a patient presented retardation of growth and lack of genital development, to accept these two phenomena as being due to a primary hypophyseal lesion, provided that cretinism, severe disorders of nutrition and other conditions with general impairment could be excluded.

The knowledge gained concerning the relations between the anterior pituitary gland and the gonads, and particularly the investigations of the hormones of these glands in the urine, have made possible a better understanding and explanation of several of these syndromes. Worthy of mention in this respect are the initial discoveries made by Zondek, and Smith and Engle, showing definitely the hypophyseal-gonadal relations. Subsequently, as a result of these investigations, biological tests have appeared which allowed the identification and measure of certain hypophyseal hormones and illustrated many concepts of the physiopathology of these conditions. Based mainly on the application of these biological tests, two groups of American investigators, Varney and his collaborators (1942) (33) and Albright and his co-workers (1942) (1) established the clinical and hormonal characteristics of a new syndrome and published various observations on this subject. The former authors called it "Association of short stature,

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retarded sexual development and high urinary gonadotropin titers in women," the latter "A syndrome characterized by primary ovarian insufficiency and decreased stature. A report of 11 cases with a digression on hormonal control of axillary and pubic hair." Later, more cases, with ovarian biopsies, were presented by Wilkins and Fleischmann (1944) (34–35). These investigators called this condition "ovarian agenesis."

The observation of various patients, whose clinical histories will be presented in this paper, has allowed us to prove that their symptoms and signs parallel the characteristics of this new syndrome.

The biopsies obtained from six of these patients showed only the existence of rudimentary ovarian structures, and in none of the histological preparations was it possible to demonstrate differentiated elements characterizing the ovary. In all of the patients, the sexual characteristics showed evidence of estrogenic insufficiency, and repeated determinations of the gonadotropins in the urine gave titers higher than the normal range.

Since this syndrome has an anatomical basis it is highly improbable that surgeons and pathologists have overlooked it. Thus, before 1942, there appeared in the literature isolated observations on cases which undoubtedly corresponded to the syndrome of rudimentary ovary, since they showed considerable alterations in the sexual organs as proved by laparotomies and necropsies.

Nevertheless, these publications certainly do not diminish the merits of the work of Varney, Albright and their respective co-workers, since these investigators were the first to explain these cases by means of biological tests, indispensable in our opinion, to verify the diagnosis. These authors have classified with a clinical approach a group of patients, suffering from obvious endocrine disturbances, and set up the basis for their treatment. It may be added that this new clinical picture has helped to understand and apply to human beings a great part of the knowledge gained in experimental endocrine physiology.

The observations previous to 1942 which, we might say, correspond to the anatomical period of the syndrome, may be divided into two groups:

a) Those gained at necropsies.

b) Those obtained at laparotomies.

Table 1 contains a summary of the bibliographic indications together with the diagnostic elements of both groups. It concerns twenty observations that appeared between 1912 and 1941, thirteen of which correspond to the necropsy group and seven to the group of biopsies.

This series of cases belongs to the period during which each author reported the result of his experience on a merely anatomical basis. It was not until later, as has already been mentioned, that publications appeared which no longer dealt with scattered cases but with series of cases which

TABLE 1

Observation No.	Author and year	Necropsy or biopsy	Age	Height in cm.	Menstruations	Mammary glands	Hair		Ovaries	
							Public	Axillary	Macroscopical examination	Histological examination
1	Kermauner, F. (12) (1912)	Biopsy	24	short	0	+	+	0	Filiform formations, 3×5 cm long	—
2	Ranson (22) (1913)	Biopsy	27	135	0	0	0	0	Have not been found	—
3	Clivet (17) (1923)	Necropsy	38	148	0	0	+	+	Have not been found	—
4	Schultze (25) (1923)	Necropsy	30	—	—	0	++	++	Have not been found	—
5	Sellheim (28) (1924)	Biopsy	21	161	0	0	+	0	2.5×7.5 mm in size	Primordial follicles and interstitial cells
6	Randerath (21) (1925)	Necropsy	61	145	0	0	+	+	Only a thin whitish fold	Ovarian tissue has not been encountered
7	Schürmann (26) (1927)	Necropsy	25	143	0	0	0	0	Have not been found	—
8	Baer, W. (2) (1927)	Biopsy	23	Æ	0	0	+	0	—	Lack of differentiated elements; cells similar to those of the glomerular zone of the adrenal cortex
9	Herxheimer (10) (1929)	Necropsy	—	—	—	—	—	—	Have not been found	—
10	Rössle and Wallart (24) (1930)	Necropsy	39	133½	0	0	0	0	Filiform formations	Lack of differentiated elements. Nodules of the adrenal cortex of Marchand and sympathetic cells
11	Kuliga (14) (1930)	Biopsy	25	176	0	0	+	+	Have not been found	—
12	Meyer, R. (16) (1931)	Biopsy	26	169	0	0	+	+	Filiform formations	Lack of differentiated elements
13	Prusel (20) (1931)	Necropsy	45	137	0	0	±	0	Have not been found Tuberculous peritonitis	
14	Goldwasser (9) (1933)	Biopsy	23	141	0	0	0	0	Filiform formations	Absence of differentiated elements
15	Pela (18) (1935)	Necropsy	36	185	0	0	±	0	Formations of the size of the seeds of oranges	Lack of differentiated elements
16	Tronci (31) (1938)	Necropsy	20	153	0	0	±	0	Formations 6×2.5 mm large	Germinative epithelium. Lack of primordial follicles
17	Pich (19) (1938)	Necropsy	18	137	0	0	±	0	Filiform formations	Lack of differentiated elements
18	Pich (19) (1938)	Necropsy	49	155	0	0	±	0	Filiform formations	Interstial cells. Primordial follicles have not been found
19	Pich (19) (1938)	Necropsy	29	163	0	0	0	0	Right ovary 28×5×3 mm. Left ovary 30×4×2 mm.	Germinative epithelium and some primordial follicles
20	Sharpey-Shafer(29) (1941)	Necropsy	21	145	0	0	±	0	Have not been found Tuberculosis of peritoneum	—

may be included in the new syndrome for anatomical, physiopathological and clinical reasons.

Review of the literature and careful study of the results of the observations permit us to describe the anatomical, biological and clinical manifestation of the "Rudimentary Ovary" syndrome, as follows:

a) The patients are generally of short stature of moderate degree.

b) Primary amenorrhea is present.

c) The breasts have not developed, the external genitalia have an infantile appearance, and the uterus is hypoplastic.

d) The pubic and axillary hair is almost always diminished and sometimes absent.

e) The anatomical study of the ovary shows its rudimentary condition.

f) The hypophyseal gonadotropins are always increased in the urine.

g) The estrogens in the urine show subnormal titers.

h) The neutral 17-ketosteroids of the urine are diminished.

i) The vaginal smears are of the atrophic type.

j) There are the following alterations in the skeletal system:

1) delay in aging of bone,

2) diffuse osteoporosis,

3) vertebral chondrodystrophia.

k) Congenital anomalies have been mentioned in certain cases: webbing of the neck, cubitus valgus, syndactylism, coarctation of the aorta, etc.

In order to establish the clinical diagnosis of this syndrome, it is necessary to find the following combination of symptoms: primary amenorrhea, increase in urinary hypophyseal gonadotropins and the presence of the other manifestations produced by estrogenic insufficiency.

The diagnosis becomes indubitable when the histological study discloses the existence of rudimentary ovaries. Yet we must admit that this histological finding is not essential and that it is possible to reach the same result by means of the clinical elements and the biological tests mentioned above.

MATERIAL AND METHOD

The hypophyseal follicle-stimulating-hormone (F.S.H.) in the urine was measured by Zondek's method with the modifications introduced by Albright and his co-workers (1943) (13). In order to determine the titers of the F.S.H., one of its biological properties was used, the power to increase the weight of the uterus of the prepuberal female mouse following estrogen liberation from its own ovary. With this method the F.S.H. titers were established corresponding to those of normal women as well as the increases and decreases observed in different conditions. It has been settled that normal adult women have more than 6 mouse units and less than 96 mouse units in the urine per 24 hours.

The urinary estrogens were measured according to D'Amour and Gustavson's method (1930) (7). It is considered that the urine excreted in 24 hours by normal adult women contains from 30 to 160 I.U.

For the determination of the neutral 17-ketosteroids in the urine Zimmermann's method (1936) (36) was employed with the modifications introduced by Callow and his co-workers (1939) (4). The values indicated correspond always to the urine per 24 hours. Twelve to eighteen mg. are considered to be normal values for the adult woman in this period of time.

In order to perform the insulin tolerance test, the instructions given by Reifenstein (1944) (23) were followed. One tenth unit of regular insulin per kilogram of ideal weight was administered and samples of the blood were taken while fasting and 20, 30, 45, 60, 90 and 120 minutes after the injection.

The clinical histories of eight patients are presented; only the interesting features and the biological findings considered to be of value for the characterization of the syndrome under discussion are reported.

Case 1.—T.R., 19 years of age, was transferred to us by a physician because of lack of menstruation and insufficient development of her secondary sexual characteristics. The physical growth had been normal, and it had never been noted that she was short, as compared with other girls of the same age. When she was 14, scanty pubic hair appeared but no axillary hair was noted. The breasts remained infantile. At that time the patient's personality altered, she became irritable; abnormal and involuntary movements of the muscles of the face appeared, and she had some difficulty in picking up objects. These disorders, which at the beginning had been noticed only once a day and which were of short duration, increased in intensity and occurred several times a day, obliging her to stay in bed for three months (Sydenham's chorea?). Treated with injections, the composition of which she does not know, she improved gradually until the trouble disappeared almost completely.

Born at full term, she had been breast fed by her mother. She began talking at the usual age. She did not remember being ill during her childhood. At the age of 7, she fell from a 3-meter height and was unconscious for several hours. She entered school at the age of 6, and went on for two years, showing some difficulty in retaining what she had learned.

She did not suffer from physical or psychical asthenia, nor from impairment of vision. At the age of 18, she was treated with injectable medicines and after a few months' treatment, a slight and painless bloody discharge from the vagina was observed which lasted only two days.

Her father, a chronic alcoholic, suffers from pulmonary T.B.C. She has 7 brothers and 7 sisters, all of them apparently healthy. The sisters show normal development.

PHYSICAL EXAMINATION: Height 166 cm., span 166 cm.; weight 55 kg. Well nourished girl.

Pilous system: Lack of axillary hair; mons veneris: hair very scanty, forming a thin stripe.

Bone system: Cubitus valgus on the left. Increased pronation of the feet. Partial syndactylism of two toes of the right foot.

Mammary glands: Lack of glandular tissue; very scanty fatty tissue; infantile nipples and areolae (Fig. 1).

Circulatory system: Normal; blood pressure 110/70.

Genitalia: Hypoplastic vulva; labia minora and clitoris small. Hymen preserved. Perineum excavated. Vaginal discharge of an alkaline reaction. Rectal examination: long vagina at the end of which a small stump the size of a thimble is felt, corresponding to a very slightly developed uterus. The ovaries are not felt.

Roentgenograms revealed accentuated carpal osteoporosis; normal spine; small sella

FIG. 1. *Case 1.—T. R.*, 19 years of age, height 166 cm.

turcica; epiphyses of the cubitus, metacarpal bones and knees not united, i.e., persistent conjugation cartilages (Fig. 2 & Fig. 3).

LABORATORY DATA: Hypophyseal follicle-stimulating-hormone (F.S.H.)
Nov. 10, 1945, positive for 96 mouse units in the urine per 24 hours.
Nov. 27, 1945, positive for 96 mouse units in the urine per 24 hours.
Nov. 30, 1945, positive for 96 mouse units in the urine per 24 hours.

Aschheim-Zondek test in rats: negative.

17-ketosteroids: Nov. 1945: 7.2 and 12 mg. in the urine per 24 hours.

17-ketosteroids and alarm-reaction for surgical intervention:
Before the operation: 7.2 mg.
After the operation: first day, 14.9 mg.; second day, 12 mg.; fourth day, 5.9 mg.

17-ketosteroids and administration of chorionic gonadotropins:
Before: 12 mg.

After receiving injections of 1,000 rat units per day for five days: 15.2 mg.
Blood cell count: normal.—Blood urea: 32 mg. per cent.
Cholesterol: 131 mg. per cent; 200 mg. per cent; 156 mg. per cent (in three successive blood tests).
Wassermann and Kahn: negative.

FIG. 2. *Case 1.—T. R.*, 19 years of age. Persistence of the conjugation cartilages in the epiphyses of the cubitus and radius, in the metacarpal bones and phalanges. Delay in bone age and osteoporosis of the carpus bones.

Urine: Density: 1.025; acid reaction. Absence of pathological elements.
Renal concentration test: Highest density: 1.032
Robinson, Power and Kepler test: negative.
Carbohydrate metabolism: Exton-Rose test: fasting 64 mg. per cent; after 30 min. 95 mg. per cent; after 60 min. 103 mg. per cent.
Insulin tolerance curve: fasting 99 mg. per cent; 20 min. 52 mg. per cent; 30 min.

53 mg. per cent; 45 min. 88 mg. per cent; 60 min. 99 mg. per cent; 90 min. 105 mg. per cent; 120 min. 99 mg. per cent.

Vaginal smears: Atrophic.

OCULAR FUNDUS AND VISUAL FIELD: normal.

FIG. 3. The same patient as in Fig. 2. Persistence of the conjugation cartilages and osteoporosis.

VAGINOSCOPY: pink mucous membrane with whitish secretion. Cervix with a smooth mucous membrane, external orifice very small and round.

SURGICAL INTERVENTION: The patient underwent operation for chronic appendicitis, during which it was noted that the uterus was composed of a thickening of muscle tissue, the size of the fleshy tip of the fore-finger; the tubes were thin and increased in length; the ovaries consisted of two whitish cords, the same calibre as the tubes. A right ovariectomy was undertaken.

HISTOLOGICAL EXAMINATION: Specific elements of the ovary are not found; only in the cortical region a stroma is noted, ovarian in appearance, but fibrous, such as may be observed on the senile involutive ovaries. A few small ducts are seen to have a cuboidal epithelium, which has nothing to do with the elements peculiar to the ovary and which corresponds perhaps to celomic inclusions (Fig. 4).

HISTOLOGICAL DIAGNOSIS: Rudimentary ovary.

Summary of Case 1.—Normal growth, bone age retarded, primary amenorrhea, infantile mammary glands, pubic hair very scanty, axillary hair had never developed, hypoplastic vulva, infantile uterus, vaginal smears without estrogenic response, 17-

FIG. 4. Section of ovarian tissue (*Case No. 1, T. R.*). Specific elements are not observed. In the cortical zone stroma of ovarian appearance of the senile involutive type.

ketosteroids diminished, urinary gonadotropins (F.S.H.) increased on several determinations. Syndactylism of the toes, cubitus valgus. The biopsy disclosed absence of the characteristic elements of the ovary.

Case 2.—*L.T.R.*, 18 years of age, was first seen in November, 1945, because of lack of sexual development and retardation of growth.

During the school age, she had always been one of the smallest girls, and though she grew later on, her body height had always been shorter than that of her school friends of the same age. Her parents and uncles are of rather tall stature.

Only daughter; born at full term; fed with artificial lactation; began walking at the age of 20 months and talking with some delay. She had measles at the age of 10, and epidemic parotitis when she was 9. At the age of 14, she noted the appearance of thin

pubic and axillary hair, but very scanty. At the same time, a slight increase in the size of the breasts was noted. Until the present time there have been neither menstrual cycles nor bloody genital discharges. She does not complain of "hot flashes"; she has neither visual disorders nor headaches. She is not nervous and her psyche is normal, though rather infantile. She does not suffer from physical or psychic asthenia. She had received no treatment before she came to the hospital.

PHYSICAL EXAMINATION: Height 145 cm.; span 152 cm.; weight 40 kg. She is fairly well nourished. Her facial appearance is that of a much older person (Fig. 5).

FIG. 5. *Case 2, patient L. T. R.* Shows the accentuated cubitus valgus, just as described by Turner.

Pilous system: On the skin of the shoulder and arms the hair is abundant. The axillae show scanty hair; a small amount of pubic hair with feminine distribution is noted.

Skeleton: Cubitus valgus, more accentuated on the right side; scoliosis and slight vertebral lordosis; the 6th and 7th dorsal vertebrae are depressed and painful on pressure. Pes cavus at rest. Left foot in marked pronation. Articular lassitude.

Mammary glands: Lack of glandular tissue, very little fatty tissue, areolae and nipples infantile.

Genitalia: Vulva and labia majora hypotrophic with scanty hair reaching the peri-

neum. Abundant vaginal discharge, labia minora deficiently developed, except for the portion near the prepuce of the clitoris. Clitoris of a larger size than normal. Hymen preserved. A small nodule corresponding to a very hypoplastic uterus is felt per rectum.

Vaginoscopy: (done with the urethroscope): Pink mucous membrane, small cervix with a smooth mucous membrane, adolescent type.

Roentgenograms revealed accentuated chondrodystrophia of the dorsal vertebrae, epiphyses not united with the vertebrae; sella turcica normal; the skull with the diplos very thin, and non fusion of epiphyses in the wrists and shoulders. Vertebral and iliac osteoporosis. Osseous development: less than 18 years (Fig. 6–7).

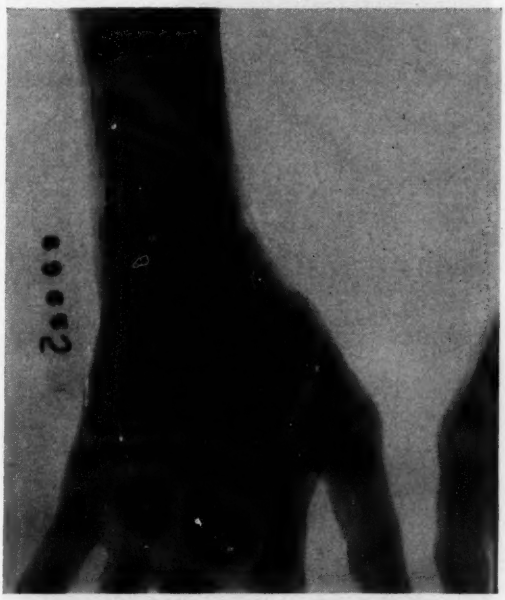

FIG. 6. *Case No. 2.—L. T. R.*, 18 years of age. Delay in bone age.

LABORATORY DATA: Hypophyseal follicle-stimulating-hormone (F.S.H.)
Nov. 27, 1945, positive for 96 mouse units in the urine per 24 hours.
March 12, 1946, positive for 96 mouse units in the urine per 24 hours.
Aschheim-Zondek test: negative.
17-ketosteroids: April 17, 1946, 24.1 mg.; second sample 28 mg., May 8, 1946, 16.3 mg.; May 13, 1946, 16.9 mg.
Urinary estrogens: negative for 24 I.U. (2 rat units) in the urine per 24 hours.
Blood cell count: normal.—Blood cholesterol: 153 mg. per cent.
Blood urea: 25 mg. per cent.—Wassermann and Kahn Tests: negative.
Urinary creatine[1]: 219 mg. per 24 hours.

[1] The creatine and creatinine values refer in all patients to 24 hour samples.

Creatinine: 89 mg. Creatinine Index: 23.2.
Carbohydrate metabolism: Exton-Rose test: fasting 116 mg. per cent; after 30 min. 120 mg. per cent; after 60 min. 147 mg. per cent.
Insulin tolerance curve: fasting 98 mg. per cent; after 20 min. 54; after 30 min. 46; after 45 min. 60; after 60 min. 83; after 90 min. 89; after 120 min. 72 mg. per cent.

FIG. 7. The same patient as in Fig. 6. Accentuated chondrodystrophia of the dorsal vertebrae. Vertebral epiphyses not united.

Basal metabolic rate: +41 and +28 per cent in two determinations.
Urine: Alkaline reaction. Density: 1.012. Abundant urobilin and microorganisms.
Test for highest renal concentration: density 1.027.
Robinson, Power and Kepler Test: negative.
Vaginal smears: atrophic.

OCULAR FUNDUS: normal. Campimetry: narrowing of the visual fields.

SURGICAL INTERVENTION: Laparotomy with Pfannenstiel's incision. Broad ligaments very thin; very small uterus (4–5 cm. long). At the sites corresponding to the ovaries two

cords of whitish color are noted, ½ cm. in diameter. The right adnexa is removed for biopsy.

HISTOLOGY: medullary (Dr. Colillas): What should be the ovary is a rudimentary cortex and a medullary zone very rich in vessels. On the border of a section of the tube, a small conglomerate of cells is noted, possibly an inclusion of aberrant cells of the adrenal cortex. Tube hypoplastic. Müllerian and Wolffian residues and a nerve rim surrounded by a cover of sympathetic cells are seen. Lack of differentiated elements of the ovarian parenchyma (Fig. 8).

HISTOLOGICAL DIAGNOSIS: Rudimentary ovary. Adrenal inclusions.

FIG. 8. Biopsy of *Case 2* (*L. T. R.*). Cell conglomerate of the aberrant adrenal cell type. Differentiated elements of the ovary are not noted.

Summary of Case 2.—Growth moderately diminished; proportions of the skeleton similar to those in eunuchoidism; bone age delayed; primary amenorrhea. Mammary glands infantile; pubic and axillary hair diminished; vulva hypoplastic; uterus infantile; vaginal smears atrophic; urinary gonadotropins increased above normal. 17-ketosteroids increased (patient suffers from a discrete hirsutism); the insulin tolerance curve shows the reaction to hypoglycemia somewhat diminished; creatine in urine increased. Cubitus valgus; concentric narrowing of the visual fields. Rudimentary ovaries corroborated by the study of the biopsy.

Case 3.—*R. L.*, 20 years of age, was first seen in December, 1945, on account of her short stature and because she had never had menstrual periods nor genital bloody dis-

charges. She informed us that until the age of 14, she was steadily growing, but that she had always been one of the smallest among the pupils of her school-year. At fourteen she had stopped growing. When she was 15, scanty pubic and axillary hair appeared, without development of the mammary glands until the age of 19. At that age a slight increase in size had been noted. Since October, 1945, she felt occasional "hot flashes." Sometimes headaches, no visual disorders.

Born at full term, she began talking at the usual age, but walking was delayed. From the second to the ninth year she suffered from diarrheal crises with several daily evacuations, which disappeared at the age of 10. During her infancy, measles and roseola. She went to school until she was 12; at that time she finished the sixth grade, having been a rather bad pupil. She has always been strong, without feeling physical or psychical fatigue.

FIG. 9. *Case 3.—R. L.* Note the pyknic habitus and the lipodystrophy.

The parents are healthy, short in stature. A brother, aged 22, is normal and of average height.

For five months during the past five years she had been treated with thyroid preparations and thereafter with 30 injections of hypophyseal extract. Two years ago, an hypophyseal implantation had been performed. These treatments did not cause any appreciable improvement.

PHYSICAL EXAMINATION: Height 135 cm.; span 140 cm.; weight 46 kg. Fairly well nourished. Strength preserved (Fig. 9).

Pilous system: Discrete hypertrichosis on the forearms. Lack of axillary hair; the pubic hair is considerably diminished.

Mammary glands: There is no development of glandular tissue, the nipples are infantile, with abundant fatty tissue.

Blood pressure (Baumanometer) 138/78. Distribution of the fatty tissue particularly on the girdle area and anterior wall of the abdomen.

Skeleton: Pes cavus corrected simply by standing. Feet show bilateral pronation, more pronounced on the left side. Articular lassitude increased in the superior and inferior members.

Genitalia: Vulva hypoplastic, hymen preserved, some alkaline discharge. A small stump is noted by rectum which seems to correspond to a very hypoplastic uterus.

Vaginoscopy: Pink vaginal mucous membrane; very small cervix.

Anterior and lateral roentgenograms of the spine showed discrete chondrodystrophia of the dorsal vertebrae. Persistence of the conjugation cartilages of the phalanges and inferior extremity of the cubitus and radius; sella turcica normal. Very discrete osteoporosis. Bone age: less than 19 years.

Laboratory Data: Hypophyseal follicle-stimulating-hormone (F.S.H.):
Nov. 18, 1945, positive for 96 mouse units in the urine per 24 hours.
Dec. 18, 1945, positive for 96 mouse units in the urine per 24 hours.
April 4, 1945, positive for 96 mouse units in the urine per 24 hours.

Aschheim-Zondek Test: negative.

17-kestosteroids: Dec. 1945: 9 mg. in the urine, per 24 hours; May 8, 1946: 8 mg. in the urine, per 24 hours.

17-ketosteroids and alarm-reaction for surgical intervention:
Before the operation: 8.9 mg.
After the operation: first day 9.2 mg.; second day 14.6 mg.; third day 13.9 mg.; fourth day 5.5 mg.

Urinary estrogens: negative for 24 I.U. in the urine per 24 hours.

Blood cell count: normal.—Cholesterol: 153 mg. per cent.

Urea: 27 mg. per cent.—Renal concentration test: 1.032.

Creatine in urine: 400 mg. per 24 hours.

Creatine + creatinine: 560 mg. per 24 hours.

Creatinine coefficient: 11.4.

Wassermann and Kahn: negative.—Urine examination: density 1.026 normal.

Carbohydrate metabolism: Exton-Rose test: in fasting 98 mg. per cent; after 30 min. 115 mg. per cent; after 60 min. 120 mg. per cent.

Insulin tolerance curve: Fasting 94 mg. per cent; after 20 min. 53; after 30 min. 71; after 45 min. 56; after 60 min. 58; after 90 min. 74; after 120 min. 62 mg. per cent.

Vaginal smears: Atrophic on several examinations.

Ocular Fundus: normal. Visual fields concentrically narrowed.

Surgical Intervention: Pfannenstiel laparotomy; broad ligaments very thin, nearly transparent. The uterus has the form of an hour-glass, 4–4½ cm. long; the round ligaments are scarcely visible; the tubes are large but very thin with very small pavilions. Beneath the pavilions some whitish cords are noted, ½ cm. thick, corresponding to the ovaries. The right adnexa is removed. An appendectomy is performed.

Histological Examination: (Dr. Colillas): Some celomic cysts are observed within a fibrous stroma. In these cysts the theca layer is not visible. In several zones specific

stroma, somewhat fibrosed, are observed. Ovarian follicles are not noticed. Tubes of essentially normal appearance and congestion of their walls.

HISTOLOGICAL DIAGNOSIS: Rudimentary ovary.

Summary of Case 3.—Accentuated decrease in stature with proportions of the skeleton similar to those of eunuchoidism; primary amenorrhea, lack of mammary glands; scanty pubic and axillary hair; hypoplastic vulva; infantile uterus; atrophic vaginal smears; urinary gonadotropins increased on repeated determinations; 17-ketosteroids diminished; vertebral chondrodystrophia and diffuse osteoporosis; creatine in the urine increased; creatinine coefficient diminished; the insulin tolerance curve shows that the reaction to hypoglycemia is also diminished; there are no congenital malformations; ocular fundus normal; concentric narrowing of the visual fields. The histological study discloses the absence of the characteristic elements of the ovary.

Case 4.—R. V., 14 years of age, came to our Service having noticed that she had stopped growing during the last 3 years and that her sexual development was abnormal.

Since childhood, her stature has been shorter than that of her companions of the same age, and she occupied always the first place among the girls of her school-year. She passed regularly through the primary school and followed as a good pupil the superior course of the Commercial School. At the age of 13, pubic and axillary hair of scanty quantity appeared. Never has she had menstruations; her mammary glands developed very little. A year ago hot flashes appeared in an irregular manner, two or three times a day.

Born normally at full term, walking and talking occurred at the normal age. At the age of 16, she had diphtheria with subsequent paralysis of the soft palate. Her father is healthy, 180 cm. tall; her mother, 162 cm.

The patient was treated in 1944 with hypophyseal extract, 1 cc. three times a week for 2½ months. At the same time, estrogen containing pomades were applied to the breasts. An increase in their volume and pigmentation of the nipples were noted with this treatment.

In April, 1945, she was treated with hypophyseal and adrenal extracts for one month. She believes that in the last year she has grown two centimeters.

PHYSICAL EXAMINATION: Height 140 cm.; span 142 cm.; weight 47.2 kg. Fairly well nourished. Facial appearance according to her age. Slight obesity of the anterior wall of the abdomen (Fig. 10).

Pilous system: The axillary hair is very scanty. The pubic hair is actually developed as a result of the administration of estrogens.

Skeleton: Very exaggerated bilateral cubitus valgus.

Mammary glands: in both breasts glandular tissue of the size of a nut is felt (which has appeared after the local application of estrogen-containing pomades). Nipples and areolae very pigmented.

Circulatory system; Arterial pressure 125/78 (Baumanometer).

Genitalia: External genitalia hypoplastic, more accentuated on the labia minora; clitoris with normal prepuce. There is no discharge; alkaline vaginal secretion; hymen preserved. No uterus is felt per rectum, and on its anatomical site only a small cord is encountered.

Roentgenography revealed generalized osteoporosis but no chondrodystrophia. The rest of the ilium was not united. Bone age corresponded to that of an 18 year old.

LABORATORY DATA: Hypophyseal follicle-stimulating-hormone (F.S.H.):

Nov., 1945, positive for 96 mouse units in the urine per 24 hours.
Dec., 1945, positive for 96 mouse units in the urine per 24 hours.

17-ketosteroids: 6 mg. in the urine per 24 hours.—Another determination: 6.5 mg. in the urine per 24 hours.

Postoperative alarm-reaction and 17-ketosteroids:
Before the operation: 5.9 mg.
After the operation: first day, 16.2 mg.; second day, 18.8 mg.; third day, 16 mg.; fourth day, 9.4 mg.; fifth day, 4.5 mg.

FIG. 10. *Case 4, patient R. V.* Height 141½ cm.

17-ketosteroids and administration of chorionic gonadotropins;
Before the administration: 6.5 mg. per 24 hours.
After the injection of 1,000 rat units of chorionic gonadotropins each day for 5 days: 17.1 mg.

Blood cell count: red cells 4,010,000; white cells 9,800; hemoglobin 74%.

Wassermann and Kahn reactions: negative.

Carbohydrate metabolism: Fasting glycemia: 103 mg. per cent.

Vaginal smears: Atrophic.

SURGICAL INTERVENTION: A laparatomy was performed disclosing a small uterus, 3

cm. long and 2 cm. wide; rudimentary round ligaments; very small tubes and pavilions; at the site corresponding to the ovaries, two very thin whitish cords were noted. A piece from the left side was removed.

HISTOLOGICAL EXAMINATION: (Dr. Colillas): The appearance of the stroma resembles, particularly in certain zones, that of the ovary. A series of inclusions of the epithelial or mesothelial type were observed; some adopted pseudoglandular and canalicular arrangements, others presented themselves as massive islands of cells of variable type. Some of them were interpreted as not belonging to the ovary itself (Müllerian and Wolffian ducts, etc.), and the others as specific of the ovarian pattern but disturbed in their evolution.

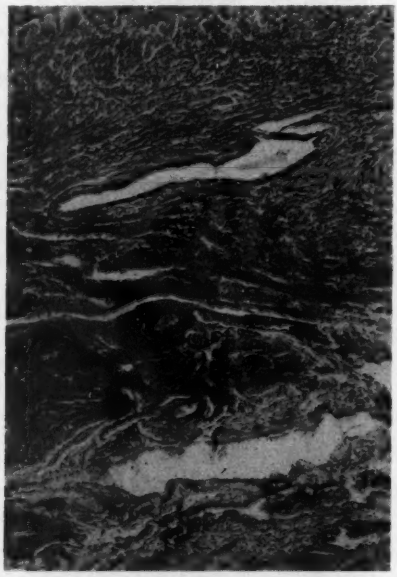

FIG. 11. *Case 4* (*R. V.*). Stroma similar to that of the ovary. Inclusions of epithelial or mesothelial type, adopting pseudo-glandular arrangements.

Several small foci were seen or noted with the characters of the specific stroma of the ovary, from which seem to generate cells with clear cytoplasm (thecal cells) (Fig. 11).

HISTOLOGICAL DIAGNOSIS: Rudimentary ovary.

Summary of Case 4.—Growth diminished since her infancy; bone age until the present time normal; primary amenorrhea; mammary glands moderately developed as a result of estrogenic treatment; pubic and axillary hair scanty; vulva hypoplastic; vaginal smears atrophic; 17-ketosteroids diminished; urinary gonadotropins (F.S.H.) increased on repeated determinations; cubitus valgus. Microscopically, the characteristic elements of the ovary are absent.

Case 5.—S. F., 22 years of age, was first seen in March, 1946, because of her short stature and lack of sexual development. The body growth continued, though slowly, until

the age of twelve and since then, she had stopped growing almost completely. She had been treated with growth-promoting hormones administered intermittently and claims to have grown several centimeters.

Until 1942, at the age of 18, there was no bloody discharge from the vagina and after that year, coinciding always with the application of injections (anterior hypophyseal lobe), she had the following episodes of bleeding: in 1942, 1943 and 1944, two little bloody genital discharges each year; in February, 1945, only several drops of blood. At the age of 15, pubic and axillary hair appeared in a small quantity. Never had she had hot flashes. Vision was normal, but she suffered from headaches of moderate intensity. She tired easily. She went to school for 3 years and was a rather bad pupil. The patient was born at full term and fed by her mother. During her early infancy she suffered in her country (Russia) from severe rickets which retarded walking till she was 3½ years old.

FIG. 12. *Case 5, patient S. F.*, 22 years of age. Senile facies.

Also dentition had been considerably retarded. She had measles at the age of 6; chronic otitis media persisted until the age of 13. She has always been considered a weak child. During the last years she suffered from diarrheal crises.

The father died at the age of 51 due to trauma; he was a tall man. Her mother was small, though taller than the patient.

PHYSICAL EXAMINATION: Stature 136 cm.; span 142 cm.; weight 48 kg. Fairly well nourished. Her facial appearance is that of a much older woman (see photograph) with periorbital wrinkles and wrinkles on the commissure of the lips (Fig. 12).

Pilous system: Thin, abundant hair. A small amount of hair on the eye-brows. Scanty axillary and pubic hair.

Skeleton; Articular cracks in the right knee. Proportions similar to those in eunuchoidism. Dorsal outward bending of the spine. Slight right cubitus valgus, incomplete

extension of the right elbow. Foot in slight pronation with depression of the arch.

Circulatory system: Normal; arterial pressure (Baumanometer) 120/70.

Genitalia: Vulva: labia majora hypoplastic; labia minora prominent in their superior portions, prepuce and clitoris well developed. Hymen preserved. Vaginoscopy; vaginal mucous membrane red; cervix small. Rectal examination: a small hard uterus (4–6 cm.) is palpated; ligaments are not.

Roentgen Rays: anterior and lateral views of spine, discrete chondrodystrophia. Epiphyses of the cubitus and radium not completely united, nor the crest of the ilium. Diffuse osteoporosis. Bone age less than 20 years.

Laboratory Data: Hypophyseal follicle-stimulating-hormone (F.S.H.).
Dec. 4, 1945, positive for 96 mouse units in the urine per 24 hours.
Dec. 5, 1945, positive for 96 mouse units in the urine per 24 hours.
March 16, 1946, positive for 96 mouse units in the urine per 24 hours.
March 18, 1946, positive for 96 mouse units in the urine per 24 hours.
Aschheim and Zondek Reaction: negative.
17-ketosteroids: April 17, 1946, 11 mg. per 24 hr.; May 8, 1946, 11.3 mg. per 24 hr.
Carbohydrate metabolism: Exton-Rose test: fasting 86 mg. per cent; after 30 min. 95 mg. per cent; after 60 min. 105 mg. per cent.
Insulin tolerance curve: fasting 82 mg. per cent; after 20 min. 56; after 30 min. 47; after 45 min. 68; after 60 min. 79; after 90 min. 79; after 120 min. 90 mg. per cent.
Blood cell count: Normal.—90 mg. per cent. Urea: 39 mg. per cent.
Cholesterol: 142 and 181 mg. per cent.—Wassermann and Kahn: negative.
Urine: normal.—Test for highest renal concentration: density: 1.032.
Creatine: in the urine per 24 hours 0.764 Gm.
Creatine + creatinine: 1.960 Gm.—Creatinine: 1.196 Gm.
Creatinine coefficient: 30.7.—Basal metabolism: +25 per cent.
Vaginal smears: atrophic.
Robinson, Power and Kepler Test: negative.

Ocular Fundus and Visual Field: normal.

Summary of Case 5.—Marked decrease in stature since her childhood; proportions similar to those of eunuchoidism; primary amenorrhea; lack of development of the mammary glands; small amount of pubic and axillary hair; bone age retarded; vulva hypoplastic; uterus infantile; vaginal smears atrophic; urinary gonadotropins increased (F.S.H.); 17-ketosteroids somewhat diminished; diffuse osteoporosis and marked chondrodystrophia of the spine; creatine increased; creatinine index normal.

Case 6.—*M. J. M.*, 17 years of age, came to see us on account of her short stature and because up to the present time she had never had menstrual periods, (Fig. 13).

Since the third year of age, it has been noted that she was undersized as compared to other girls of her age. The patient has shown us a series of photographs taken at successive dates, on which she is accompanied by other girls of similar ages; these photographs indicate that the growth has been steady, though retarded (Fig. 14). She had always been looked upon as a weak child; when she was 8, she weighed 18 kgs. At the age of 6, she had difficulty entering school on account of her small height. Until the present time, no bloody discharges from the vagina have appeared; there is no pubic or axillary hair. In 1945, she had several crises with palpitations, suffocations, hot flashes with reddening of the face, oppression in the chest and general lassitude, ending usually in a flood of

tears. These crises lasted from one to two hours and obliged her to go to bed. She tires easily, is irritable and is of easy emotivity.

Normally born at full term, she was fed by her mother for three months and thereafter by a nurse till she was 6 months old. She began talking at the age of one year; dentition and walking occurred at the normal age. She entered school when she was 8 and attended classes for six years as a good pupil. She suffered from gastro-intestinal disorders during early infancy. She had scarlet fever at 6, and measles at 9. When she was 10, she underwent a tonsillectomy and appendectomy and suffered from pneumonia.

Her father is healthy and tall, her mother's height is 155 cm. She has two sisters; one, 18 years of age, is 160 cm. tall and the other, 15 years, is 165 cm.

FIG. 13a. *Case 6. M. J. M.*, 17 years of age.

She has been treated with chorionic and blood serum gonadotropins and with thyroid preparations, which have been well tolerated. During these treatments she has had only once a scanty genital blood loss, lasting one day; yet it did not occur a second time in spite of the continued medication.

PHYSICAL EXAMINATION: Stature 131 cm.; span 127 cm.; weight 35 kg. Well nourished; white skin with slightly yellowish spots on the face. Hairy hyperkeratosis of limbs. Hair without special characteristics. Lack of axillary and pubic hair. Webbing of the neck, which we would prefer to designate as "Sphynx neck."

Skeleton: Bilateral cubitus valgus, more pronounced on the left side. Pain on pressure

in the region of the third and fourth dorsal vertebrae. Slight outside rotation of the feet.

Mammary glands: Not developed; nipples and areolae infantile.

Circulatory system: First sound reduplicated at the apex; systolic slight murmur at the apex; systolic murmur accentuated at the left interscapulo vertebral space. Absence of other signs of aortic coarctation. Blood pressure 130/80 (Baumanometer).

Genitalia: Marked hypoplasia of the external genitalia; hymen preserved. Only a small uterine stump was made out by rectal examination.

Vaginoscopy: pink vaginal mucous membrane; cervix infantiles has a wrinkled mucous membrane.

FIG. 13 b.

FIG. 13 c.

Case 6. MJM. Same patient as in 13a at the ages of 9 and 13 years, compared with her younger sister.

ROENTGEN RAYS: Anterior and lateral films of the spine: vertebral chondrodystrophic lesions. Epiphyses of cubitus, radium and phalanges not closed. Osteoporosis of the spine; cuneiform vertebrae. Skull: thin diploe; small sella turcica. Bone age less than 18 years.

LABORATORY DATA: The hypophyseal follicle-stimulating-hormone (F.S.H.).
Nov. 16, 1945, positive for 96 mouse units in the urine per 24 hours.
Dec. 22, 1945, positive for 96 mouse units in the urine per 24 hours.
March 12, 1946, positive for 96 mouse units in the urine per 24 hours.

Aschheim-Zondek Test: negative.

17-ketosteroids: April 17: 19.0 mg.; April 20, 6 mg.; April 27, 8.6 mg.; May 8, 10.5 mg.; May 13, 10.8 mg.

Blood cell count: normal.—Blood Urea: 30 and 40 mg. per cent.

Cholesterol: 238 and 250 mg. per cent.—Inorganic phosphorus: 4.70 mg. per cent.

Blood calcium: 10.6 mg. per cent.—Wassermann and Kahn: negative.

Urine: normal. Density 1.026.

Creatine: 69 mg. in the urine per 24 hours.
Creatine + creatinine: 339 mg. in the urine per 24 hours.
Creatinine coefficient: 97.
Glucose tolerance test: Exton-Rose Test: fasting 78 mg. per cent; after 30 min. 97; after 60 min. 1.04 mg. per cent.
Insulin tolerance curve: Fasting 86 mg. per cent: after 20 min. 43; after 30 min. 54; after 45 min. 50; after 60 min. 58; after 90 min. 58; after 120 min. 62 mg. per cent.
Vaginal smears: atrophic.
Examination of the feces: neutral fats and acid fats not observed. Several digested muscle fibers; absence of blood and parasites.
Basal metabolic rate: +21 per cent.
Ocular Fundus and Visual Field: Narrowing of the visual fields. Fundus normal

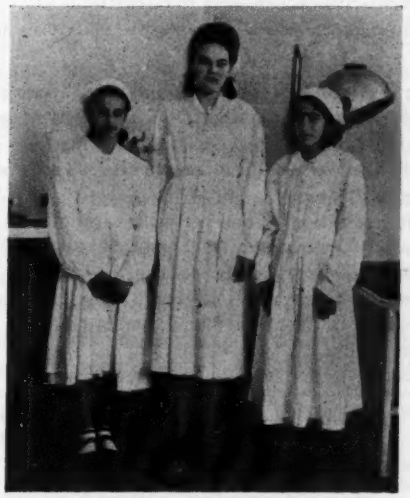

Fig. 14. Three patients (*Cases 1, 2 and 7*). The patient in the center (*Case 1*) with normal stature, and the two others with relatively reduced growth.

Summary of Case 6.—Very marked decrease in growth since infancy; primary amenorrhea; lack of pubic and axillary hair; lack of mammary glands; hypoplastic external genitalia; very small uterus; atrophic vaginal smears; increased urinary gonadotropins (F.S.H.); 17-ketosteroids diminished; diffuse osteoporosis and chondrodystrophia; creatine in the urine increased; creatinine index very increased; insulin curve hypoglycemia less than normal; webbing of the neck; cubitus valgus; narrowing of the visual fields; supposed existence of aortic coarctation.

Case 7.—*L. R. O.*, 24 years of age, entered the hospital because menstrual periods had never occurred and on account of her short stature. There was no development of the mammary glands. Pubic and axillary hair appeared at normal age. On some occasions she believes she had hot flashes which appeared spontaneously and lasted a very short

time. She has always been small. She attended school, having always been rather a bad pupil. Family history not available, as she has not known her parents. She only remembers having suffered in her infancy from measles and whooping-cough, and in 1929, she was obliged to enter a hospital for one month on account of pleurisy with effusion.

PHYSICAL EXAMINATION: Height 148 cm.; span 153½ cm.; weight 36.5 kg.

Pilous system: Scanty axillary and pubic hair.

Skeleton: Fingers and toes with trend to arachnodactylia. Very marked bilateral hallus valgus. Pronation of the left foot. Pes cavus at rest.

Mammary glands: infantile. Lack of development of areolae and nipples.

Circulatory system: blood pressure 110/70 (Baumanometer). The remainder normal.

Genitalia: infantile vulva, large labia minora at the prepuce of the clitoris; large clitoris.

Vaginoscopy: pink vaginal mucous membrane; the mucous membrane of the cervix is smooth with some irregularities which seem to be cystic.

Roentgenography showed generalized osteoporosis, epiphyses not fused and bone age of less than 19 years.

LABORATORY DATA: Hypophyseal follicle-stimulating-hormone (F.S.H.).
Nov. 3, 1945, positive for 96 mouse units in the urine per 24 hours.

17-ketosteroids: May 8, 1946, 12.1 mg.; May 13, 10.5 mg.

Carbohydrate metabolism: Exton-Rose test: fasting 98 mg. per cent; after 30 min. 103 mg.; after 60 min. 160 mg.

Insulin tolerance curve: Fasting 74 mg. per cent; after 20 min. 40; after 30 min. 44; after 45 min. 57; after 60 min. 69; after 90 min. 66; after 120 min. 72 mg. per cent.

Blood cell count: normal.—Urea: 27 mg. per cent.

Wassermann and Kahn: negative.—Cholesterol 212 mg. per cent in the blood.

Urine: normal.—Creatine in the urine: 99 mg. per 24 hours.

Creatine + creatinine: 99 mg.

Basal Metabolic Rate: +13 per cent. Vaginal smears: atrophic.

OCULAR FUNDUS: Normal except for a slight flexuosity of the arterial veins. The papilla of the right eye slightly raised at the inferior border, but it is felt that this is due to an arterial vein forming an angle at that level.

VISUAL FIELDS: Concentric and irregularly narrowed, more for red and green than for white.

SURGICAL COMPROBATIONS: An operation was undertaken for an appendicular crisis, disclosing very slender broad ligaments and a very small uterus, 4 cm. high; the round ligaments were atrophic; the tubes and pavilions very small. At the site of the ovaries, two whitish cords, ½ cm. in diameter, were observed. The right adnexa was removed.

HISTOLOGICAL EXAMINATION: (Dr. Colillas): In the ovarian portion cortical substance of regular thickness without any specific element of ovarian parenchyma; medullary zone richly irrigated by small congested veins. Some Walthard's inclusion, Very rudimentary tube. Müllerian residuals. Differentiated elements of the ovary are not noted.

HISTOLOGICAL DIAGNOSIS: Rudimentary ovary.

Summary of Case 7.—Diminished growth; proportions similar to those observed in eunuchoidism; primary amenorrhea; lack of mammary glands; diminished pubic and axillary hair; hypoplastic vulva; infantile uterus; atrophic vaginal smears; increased urinary gonadotropins (F.S.H.); slightly diminished 17-ketosteroids; diffuse osteoporosis;

diminished response to insulinic hypoglycemia. Very marked concentric narrowing of the visual fields for white and even more accentuated for red and green. The histological study disclosed the lack of characteristic ovarian elements.

Case 8.—M. C., 24 years of age, entered the hospital on account of her short stature and because she has never had bloody discharges from her genital organs.

She has always been undersized as compared to her companions of the same age. Actually she does not suffer from any disorder.

At the age of 6, she had measles, and at 8, whooping cough. She attended only the first grade in school, which she had to repeat, and thereafter she abandoned school. Information about her family is not available because her parents interned her 7 years ago into a College-Asylum.

She has good appetite; her alimentation is normal.

PHYSICAL EXAMINATION: Stature 133½ cm.; span 139 cm.; weight 40 kg ; well nourished; fatty tissue with feminine distribution Her facial appearance corresponds to a person of mediocre intelligence.

Pilous system: fine and very scanty pubic hair, increased in quantity on the labia of the vulva. Axillary hair has not developed. Discrete hirsutism of the extremities.

Skeleton: harmonical; the third toe of the left foot is very short.

Mammary glands: breasts infantile with some fatty tissue; infantile nipples and areolae.

Circulatory system: Blood pressure: 115/60. The remainder without pathological alterations.

Genitalia: Hypoplastic vulva. Clitoris of normal size. Hymen preserved. A small stump is felt per rectum corresponding to the uterus; ovaries are not felt.

Of low intelligence, corresponding to a girl of 8, with very little instruction.

ROENTGEN RAYS: of the sella turcica: normal; teleroentgenography: cardiovascular shadow small in relation to the thorax, middle arch prominent. Hands: the conjugation cartilages of the phalanges and the metacarpal bones persist. Bone age: corresponding to 18 years.

LABORATORY DATA: Hypophyseal follicle-stimulating-hormone (F.S.H.).
May 7, 1946, positive for 96 mouse units in the urine per 24 hours.
May 14, 1946, positive for 96 mouse units in the urine per 24 hours.

17-ketosteroids: May 13, 1946: 19.3 mg. in the urine per 24 hours.

Blood cell count: normal.—Urea: in the blood: 30 mg. per cent.

Glycemia: 98 mg. per cent.—Cholesterol in the blood: 192 mg. per cent.

Wassermann and Kahn: negative.

Urine: normal. Density: 1.024.

Carbohydrate metabolism: Exton-Rose test: fasting 80 mg. per cent; after 30 min. 163 mg. per cent; after 60 min. 160 mg. per cent.

Vaginal smears: atrophic.

VISUAL FIELDS: Slight retraction of the external isopter. Ocular fundus normal.

SURGICAL OPERATION: An exploratory laparotomy disclosed a very small uterus, 3½ cm. long and 1½ cm. wide, very tenuous broad ligaments, very thin round ligaments and tubes; at the site corresponding to the ovaries, only two whitish cords of a small diameter and about 3 cm. long are observed. Material for biopsy is removed.

HISTOLOGICAL EXAMINATION (Dr. Colillas): The biopsy showed a non-specific stroma,

different from that of the ovary. In none of the sections could differentiated ovarian elements be found.

HISTOLOGIC DIAGNOSIS: Rudimentary ovary.

Summary of Case 8.—Pronounced decrease in stature; proportions of the skeleton similar to those in eunuchoidism. Bone age retarded, primary amenorrhea; infantile mammary glands; very scanty pubic hair; lack of axillary hair. Determination of the F.S.H.: titers higher than normal. 17-ketosteroids, normal values. Rudimentary ovaries. Marked hypoplasia of the external genitalia.

DISCUSSION

Table 2 shows the principal characteristics of the patients whose clinical histories have been presented. A study of this table reveals that these ob-

TABLE 2

Name	Age	Height in cm.	Span in cm.	Bone age	Beginning of retardation of growth	Menstruation	Hair		Mammary glands	F.S.H.	17-ketosteroids	Bone alterations
							Pubic	Axillary				
R.T. Case 1	20	166	166	<18	No retardation	0	+	0	0	+96 mouse units	7.21 mg	Osteoporosis carpus and knee
L.T.R. Case 2	18	146	152	<18	Before the age of 6	0	+	+	0	+96 mouse units	24.06 mg	Osteoporosis of spine vertebral chondrodystr.
R.L. Case 3	20	135	140	<18	Since the infancy	0	+	+	0	+96 mouse units	6.66 mg	Generalized osteoporosis vertebral chondrodystr.
R.V. Case 4	17	140	142	18	Before the age of 6	0	++	+*	+*	+96 mouse units	5.88 mg	Generalized osteoporosis
S.F. Case 5	22	136	142	<20	Has always been short	0	+	+	+*	+96 mouse units	11.29 mg	Generalized osteoporosis, chondrodystrophies
M.J.M. Case 6	17	131	127	17	Since the age of 3	0	0	0	0	+96 mouse units	6.03 mg	Vertebral osteoporosis, chondrodystrophies
L.O. Case 7	24	148	153	>19	Has always been short	0	+	+	0	+96 mouse units	10.45 mg	Generalized osteoporosis
M.C. Case 8	24	133½	139	>18	Has always been short	0	+	0	0	+96 mouse units	19.27	

* Has been treated with estrogens or gonadotropins.

servations correspond to the syndrome of rudimentary ovaries, a fact which has been corroborated in six of them by histological studies on tissues of the genital organs removed during surgical exploration.

The age of these patients ranged from 17 to 24 years, with one exception. All of them showed retardation of growth since childhood, which was well marked at the age of puberty. Such retarded growth (see Table 1) may be appreciated from the statures of the patients, since they varied from 131 to 148 cm., in height. *Case 1* had a normal height: 166 cm., (Fig. 14).

It is difficult to settle correctly the period of life at which this disorder starts. In the majority of patients it seems to be during the school age. In *case 6*, a marked retardation of growth began at the age of 3.

According to the observations made, it is our belief that this syndrome is not necessarily accompanied by short stature, though this occurs in the

TABLE 2—*Continued*

Deformities	Ocular abnormalities	External genital organs	Vaginal smears	Genital examination	Biopsy
Cubitus valgus. Partial syndactylism of toe	Visual fields normal	Hypoplastic. Small clitoris	Atrophic	Hypoplastic uterus and tubes; at the site of the ovaries two whitish cords	Rudimentary ovaries
Cubitus valgus; talipes	Narrowing of the visual fields	Hypoplastic. Great clitoris	Atrophic	Hypoplastic uterus and tubes; at the site of the ovaries two thin cords.	Rudimentary ovaries
Talipes	Narrowing of the visual fields	Hypoplastic. Normal clitoris	Atrophic	Hypoplastic uterus and tubes; at the site of the ovaries very thin cords	Rudimentary ovaries
Cubitus valgus; talipes		Hypoplastic; clitoris normal	Atrophic	Small uterus. Hypoplastic tubes. Two cords at the site of the ovaries	Rudimentary ovaries
Cubitus valgus	Normal visual fields	Hypoplastic. Normal clitoris	Atrophic	Small uterus felt per rectum. Vaginoscopy: small cervix; red mucous membrane	
Cub. valg. Sphynx' neck; aortic coaretation	Narrowing of the visual fields	Marked hypoplasia, small clitoris	Atrophic	Small uterus felt per rectum. Vaginoscopy: small cervix; irregular mucous membrane	
Talipes	Marked narrowing visual f.; more pronounced for red and green	Hypoplasia, great clitoris	Atrophic	Small uterus; hypoplastic tubes. Ovaries: two whitish cords.	Rudimentary ovaries
	Narrowing of the visual fields	Hypoplasia, normal clitoris	Atrophic	Very small uterus. Two filiform formations.	Rudimentary ovaries

large majority of the cases. In spite of the fact that Albright, Varney and their respective co-workers ascribe a primordial importance to the retardation of growth, it must be kept in mind that the first author mentions in his publication (1942) two patients,[2] whose stature was normal and, furthermore, that in the cases observed by Sellheim (1924) (28), Kuliga (1930) (14) and Meyer (1931) (16), the body heights of the patients were 161, 176 and 169 cm., respectively.

These circumstances have influenced us in calling the syndrome "Rudimentary ovaries with estrogenic insufficiency and increase in gonadotropins," whereas Albright and his collaborators, as well as Varney and his co-workers include the retardation of growth in the titles of their respective papers.

Although up to the present time the pathogenesis of the retarded growth in this syndrome has not been elicited, there are several theories for its explanation. Because of the fact that the epiphyses in these patients fuse later than normally, it is impossible to ascribe this disorder to a precocious closure of the conjugation interspace. The retardation of growth would appear to be logically related:

1) to the failure of some of the usual growth stimulants, or

2) if these stimulants act in a normal way, the conjugation cartilages do not respond as they do usually.

Accepting both hypotheses, this disorder could be a result of solely genetic factors or of secondary endocrine alterations as a result of ovarian hormone deficiency. Varney, Wilkins and their respective co-workers (1942) admit the genetic factors, whereas Albright and his group favor the hypothesis that the retardation of growth is due to a diminution of the cortico-adrenal function. This diminution would appear to be a consequence of a reduced hypophyseal stimulation which, in turn, is the result of a diminution in estrogen.

Other fundamental manifestations of this syndrome are hypoplasia of the genitalia and primary amenorrhea. All our patients showed modifications of the sexual characteristics. None of them had had spontaneous menstruation; in two (*cases 1* and *5*) blood losses from the vagina took place as a consequence of treatments not clearly specified. The mammary glands were infantile, with lack of glandular tissue and without development of the areolae and nipples. In two patients (*cases 4* and *5*) some glandular development was observed as a result of treatments with estrogenic substances.

The external genitalia were hypoplastic in all the cases. The clitoris was normal in *cases 1, 3, 4, 5, 6* and *8*, and increased in size in *cases 2* and *7*.

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[2] One of us (de la Balze) has had the opportunity to observe these patients.

On the majority of patients vaginoscopies had been performed with Luy's urethroscope; it was noted that the vaginal mucous membrane was normal and the cervix very small, as well as the external orifice. In one of the patients (*case 6*), the mucous membrane of the cervix was infantile, whereas in the others it was smooth, similar to that observed after puberty. Vaginal smears performed on different dates were atrophic in type, disclosing lack of estrogenic stimulation.

These findings, typical of childhood, in these patients, prove that changes in the secondary sexual characteristics such as are ascribed to ovarian activity, had not taken place at the time of puberty.

As to the pubic and axillary hair, in *case 6* only was the complete lack of pubic and axillary hair noted. In 6 patients the pubic hair was scanty; axillary hair was absent in *cases 1* and *8*.

From the foregoing it may be seen that same discrepancy exists between the secondary sexual characteristics and the development of pubic and axillary hair. In order to explain this phenomenon, the theory advanced by Albright and his co-workers (1942) deserves mention. These authors consider that ovarian function *per se* neither determines the development nor governs the ulterior growth of the sexual hair, but that cortico-adrenal androgens are responsible for these modifications.

Increase in urinary gonadotropins has been disclosed in all our patients, and on repeated assays, higher titers for the hypophyseal gonadotropins in urine have been found.

No doubt, without the biological tests, it would be difficult to establish the existence of the syndrome under discussion. One must keep in mind that patients with this syndrome suffer not only from primary amenorrhea but, in addition, from all the other manifestations of estrogenic insufficiency; and under the circumstances it is interesting to find out whether estrogenic insufficiency is primarily ovarian in origin or secondary to hypophyseal gonadotropic insufficiency.

If estrogen insufficiency is primarily ovarian in origin, the F.S.H. will be increased in the urine, either because the hypophysis, in the absence of the effect of ovarian hormones "becomes unbridled," producing an exaggerated quantity of them (Albright and others), or because, when an end-organ, in this case the ovary, does not exist, the gonadotropins will be excreted in the urine in increased quantities, (Heller and others). If it were a question of a primary hypophyseal lesion, a lack or decrease of the F.S.H. in the urine would be noted. We determined the amount of estrogens in urine in only 2 patients (No. 2 and 3). In both it was diminished, i.e., less than 24 I.U. in the urine per 24 hours.

The amenorrhea, the atrophic vaginal smear, the lack of development of the mammary glands, nipples and areolae, as well as the hypoplastic

external genitalia can be reasonably ascribed to estrogenic insufficiency.

In the cardiovascular system, the blood pressure was slightly increased in *cases 2* and *3*. The figures indicated by Mac Laren (1930) (15) have been used as normal values.

In one case (No. 6), a systolic murmur was heard at the apex of the heart, which was more intense in the left interscapulo-vertebral region without other elements to establish correctly the diagnosis of aortic coarctation, such as have been noted in several of the observations made by Albright and his co-workers (1942).

All our patients showed one or several abnormalities of their skeletal structure. We recall that while describing the disorders of growth, short stature has been mentioned in *cases 2, 3, 4, 5, 6, 7* and *8*. The proportions of the body were similar to those found in eunuchoidism, i.e., the span exceeded the height in *cases 2, 3, 4, 5, 7* and *8*. This is the result of late closure of the epiphyses of the long bones with respect to the skeleton. In all 8 cases a diffuse osteoporosis existed, predominately in the vertebrae and the ilium. According to the observations of Albright and his co-workers, this osteoporosis is similar to that observed in women after the menopause, and it probably should be ascribed to estrogen deficiency.

In five patients (*cases 2, 3, 4, 6* and *7*) it is interesting to note that the lesions of the epiphyses of the dorsal vertebrae are located mainly on the joint borders, which are irregular and deformed (see the roentgenographs). Such alterations have been called "epiphysitis," but might more correctly be called chondrodystrophia, on account of their anatomical characteristics.

The roentgenographic study in five of our patients (*cases 1, 3, 5, 7* and *8*), disclosed a delay in bone age in relation to the chronological age. Keeping in mind that the ages of our patients ranged from 17 to 24, it is difficult to reach at the moment definitive conclusions concerning the extent of this delay. In *cases 2, 4* and *6*, though the bone age actually coincides with the chronological age, we are not sure whether or not in the future a delay will occur in the ossification.

In patients 2 and 3, an exaggerated articular lassitude was noted.

The following congenital abnormalities were disclosed: in *cases 1, 2, 4, 5* and *6* there was cubitus valgus, observable in several of the photographs; pes cavus at rest was noted in *cases 2, 3, 4* and *7*, and the photographic proof of one of these patients has been included (Fig. 15).

Patient No. 6 reveals the abnormality called by us "Sphynx' neck." Turner described in 1938 a syndrome of infantilism with "webbed neck" and cubitus valgus. Very probably the cases presented by this author may be included in the syndrome under discussion because of the clinical char-

acteristics, although in none of them were the urinary gonadotropins determined, or the histological study of the ovaries undertaken.

As to the metabolism of the carbohydrates, it was noted (see Table 3) that among the six patients (*cases 1, 2, 3, 5, 6* and *7*), on whom the insulin tolerance curve was performed, in three (*cases 2, 3,* and *6*) failure to recover from the hypoglycemia induced by insulin was observed. This is shown by the samples removed after 120 minutes. This abnormality has been found

FIG. 15. Pes cavus at rest, corresponding to *case 3, R. L.*

in patients who have hyperinsulinism, total hypophyseal insufficiency and cortico-adrenal insufficiency.

In the cases presented, the 17-ketosteroid assay showed reduced values. In patients *1, 3, 4, 5, 6* and *7* (see Table 2), it ranged from 5.88 to 11.25 mg., normal values in *case 8*, and showed increased values (24.06 and 28.02 mg.) in patient *2*. It might be recalled that the latter patient showed in

TABLE 3. INSULIN TOLERANCE TEST

Observation	No. 1	No. 2	No. 3	No. 5	No. 6	No. 7
Fasting	99	98	94	82	86	74
20 min.	52	54	54	56	43	40
30 min.	53	46	71	47	54	44
45 min.	88	60	56	68	50	57
60 min.	99	83	58	79	58	69
90 min.	106	89	74	79	58	66
120 min.	99	72	62	90	62	72

addition hirsutism and hypertrophy of the clitoris, and that the histological study of the tissue removed for biopsy from the site corresponding to the ovary revealed an inclusion of cells, possibly adrenal in origin. This observation would support the hypothesis of the existence of a direct relation of the increase of the 17-ketosteroids to hirsutism.

It must be kept in mind that the neutral 17-ketosteroids in the urine seem to be in the female a product of the steroids metabolism produced by the adrenal cortex. The possibility that the ovary could contribute to the production of these steroids must be discarded in our cases, because of the rudimentary condition of this organ.

While considering this question, Albright thought that the low titers of the 17-ketosteroids might be the result of adrenal cortex hypofunction which, in turn, is the result of the lack of estrogenic action.

Syndrome of Adaptation.—Phase of the *Alarm-Reaction.* Thanks to Selye's research (1946) (26) the existence of a syndrome of reaction on the body to the noxious stimuli has been revealed, the so-called "Adaptation-Syndrome." In relation to this it must be recalled that Forbes (1942) (8) showed that at the beginning of a febrile condition, after certain surgical operations and, in general, accompanying an organic lesion, the urinary 17-ketosteroid assays show certain modifications. During the first days, they are increased above normal, falling thereafter below the normal level. Similar results have been obtained by other investigators, (Stevenson, Schenker and Browne, 1944 (30); Cope, Nathanson, Rourke and Wilson, 1943 (6)). In general, it is accepted that these modifications in the 17-ketosteroid values represent one of the manifestations of the so-called alarm-reaction.

In three of our patients the behavior of the 17-ketosteroids was studied during the days following surgical procedure. The patients responded with a curve similar to that of normal persons under similar conditions (Forbes, 1942) (see Table 4). It can be seen that the only difference is due to the fact that the pre-operative values were lower than those observed in normal individuals.

As a result of these findings it may be said that presumably the mechanisms involved in this reaction (de la Balze, 1946 (3)) show the same response in patients with the syndrome of rudimentary ovaries as in normal individuals.

The visual field was tested in seven of the patients (Dr. R. Gil). In two cases (*1* and *5*) the findings were normal. In four cases (*2*, *3*, *6* and *8*), a slight concentric narrowing of the isopters, corresponding to the perimetry and visual fields, was noted. In *case 7* (see field chart No. 1), the narrowing is very accentuated, particularly in the internal isopters. On

this patient, a study of the visual fields with respect to the red and green colors was made revealing a more marked narrowing of it than for the white color. In order to determine the cause of this disorder, an encephalogram with injection of air was taken (Dr. Dowling); several films showed normal pictures.

The visual field disorders observed on various patients who had the syndrome of rudimentary ovary could perhaps be ascribed to a process of arachnoiditis or a condition of another nature compressing the optic ways

TABLE 4

Date	Levels of 17-Ketosteroids		
	Case No. 1	Case No. 3	Case No. 4
Previous to operation	7.2 mg.	8.9 mg.	5.9 mg.
First day after operation	14.9 mg.	9.2 mg.	16.2 mg.
Second day	12 mg.	14.6 mg.	18.8 mg.
Third day	—	13.9 mg.	16 mg.
Fourth day	5.9 mg.	5.5 mg.	9.4 mg.
Fifth day	—	—	4.5 mg.

Study of the 17-ketosteroids previous to an operation and during the first five days after that operation. The levels are similar to those observed in normal individuals, but the initial and terminal values are lower.

in the neighborhood of the chiasm. In spite of this hypothesis, in one of our cases presenting the most accentuated lesions the encephalogram disclosed normal findings.

Six patients (*cases No. 1, 2, 3, 4, 7* and *8*) underwent laparotomies on account of intercurrent conditions; these interventions allowed the study of the internal genitalia and the extirpation of specimens for biopsy, (see Table 2). The macroscopical examination of these organs revealed in all patients a considerable delay in development. The uterus, tubes, broad and round ligaments were all reduced in size and hypoplastic in character. At the site corresponding to the ovaries, two whitish cords, increased in length and small in diameter, were encountered, (Fig. 16). In *cases 5* and *6*, a very small uterus was felt per rectum, but it was not possible to feel the adnexae.

DIAGNOSIS

The patients consult the physician because bloody discharge from the genital organs has not appeared although they have passed puberty, some of them several years ago. Furthermore, in the majority of the patients, but not in all of them, an evident delay in growth is noted.

On physical examination, in addition to the anamnestic data mentioned, the very marked failure in the development of the sexual characteristics is noted as an expression of estrogenic insufficiency. In all the cases the urinary gonadotropin titers are above the normal level.

Based upon these clinical findings, it is possible to establish correctly the diagnosis of syndrome of rudimentary ovary.

Notwithstanding, before this conclusion is reached, it is necessary to find out if the genital organs have been removed during the prepuberal

FIG. 16. Drawing made during the surgical intervention of *case 3, R. L.* The small size of the uterus and the hypotrophy of the round ligaments, tubes and broad ligaments are observed. Underneath the pavilions two whitish cords are seen corresponding to the rudimentary ovaries.

age for any condition requiring castration. This situation can be ruled out by the physician if a careful interrogation and a watchful physical examination are undertaken.

The diagnosis of this syndrome can be established by means of the anamnestic data, the physical examination and the determination of the urinary gonadotropin titers. The cases observed by Albright (1), Varney (33), and our own eight cases corroborate this statement.

Neither a laparotomy, which allows the observation of the development of the internal genitalia, nor the histological study of the tissues removed for biopsy are essential to establish the diagnosis, though they confirm it undoubtedly, thus giving an anatomical basis.

Once the characteristics of the syndrome are established and the disorders from which the patients suffer are studied, it is imperative to differentiate the clinical picture from that of other conditions disturbing growth and modifying the development of the sexual organs.

We refer first of all to the infantilisms which are a consequence of intense and prolonged nutritional deficiencies in children. In such cases the anamnestic data disclose the existence of evident quantitative and qualitative nutritional insufficiencies. The latter have not occurred in our cases.

Nor is it a question of infantilism accompanying severe condition of the digestive tract, kidneys and cardiac system, or those observed in certain illnesses with hepatosplenomegaly, in Schüller-Christian's syndrome, in Lobstein-Eddowes' disease, in Rothmund-Werner's syndrome or in parathyroid dwarfism; these affections show signs and symptoms which allow their differentiation (del Castillo and co-workers, 1944 (5)).

The possibility of a hypothyroid infantilism can be ruled out, since our patients showed neither the clinical manifestations nor the corresponding findings of the biological tests or of the complementary examinations which would allow corroboration of the presence of this condition.

The most difficult differential diagnosis to be made, in these cases of rudimentary ovaries which present diminution of growth, is that of the so-called "hypophyseal dwarfs."

In order to facilitate the differentiation between the syndrome under discussion and hypophyseal dwarfism, the following comparative Table has been made:

Rudimentary ovaries	*Hypophyseal dwarfism*
1) Women of short stature.	1) Dwarfs.
2) Infantile mammary glands and genital organs.	2) The same.
3) Development of pubic and axillary hair.	3) Lack of pubic and axillary hair.
4) Well nourished and strong.	4) Weak and easily tired.
5) Bone age some years retarded.	5) Very marked delay in bone age.
6) Late closure of the epiphyses.	6) Lack of closure of the epiphyses.
7) Very frequently vertebral chondrodystrophia.	7) The same.
8) Follicle-stimulating-hormone increased in the urine.	8) Lack of follicle-stimulating hormone.
9) 17-ketosteroid somewhat diminished.	9) 17-ketosteroid considerably diminished.

10) Normal insulin curve.	10) There is no response to insulinic hypoglycemia.
11) Congenital abnormalities; among them aortic coaractation and "Sphynx' neck."	11) Not observed.
12) Diffuse osteoporosis and early senility.	12) Not observed.
13) Normal sella turcica.	13) Pathological modifications may be observed.
14) Visual fields: some functional alterations.	14) Abnormalities in the presence of a neoplastic lesion.

It is necessary to point out clearly that the differential features indicated in this Table refer particularly to the cases of dwarfism and infantilism associated with a hypophyseal lesion of the organic destructive type; in the so-called "hypophyseal dwarfs" without apparent hypophyseal lesions, the differentiation would be very difficult if biological methods were not available which allow urinary gonadotropin assays.

We insist on the fundamental fact that in the case of a syndrome such as results from an organic hypophyseal lesion, the urinary gonadotropin assays show titers lower than the normals whereas in the cases under discussion, the determinations always showed titers above the normal levels. This fact, established in human pathology is, as has been mentioned, in accordance with experimental research; a vast literature exists on the subject.

SUMMARY

Eight cases corresponding to the syndrome designated as "Rudimentary Ovary with Estrogenic Insufficiency and Increase in Gonadotropins" have been presented.

In six cases the histological study of the ovaries and the macroscopical examination of the internal genital organs has been performed.

These new observations help to establish in a categorical manner the existence of this new syndrome described for the first time and simultaneously by Varney, Kenyon and Koch (1942) and Albright, Smith and Fraser (1942).

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TREATMENT OF CARCINOMA OF THE HUMAN BREAST WITH TESTOSTERONE PROPIONATE:[1] A REPORT OF FIVE CASES

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THE relationship of sex hormones and neoplasms has been the stimulus for a great deal of investigation in recent years. Loeb and his associates (8, 9) using mice as experimental animals, demonstrated a definite relationship between estrogenic hormone and mammary carcinoma. By means of castration they were able to decrease the incidence of spontaneous carcinoma of the breast in mice. Lacassagne (6) in 1936 and Suntzeff, et al. (12) in 1936 lowered the tumor age and increased the tumor incidence of breast carcinoma in various strains of mice by using estrogenic substance. Clinically, withdrawal of estrogen by surgical or roentgen castration as an adjunct in the treatment of carcinoma of the human breast is an old and acceptable procedure (2).

Following Lacassagne's (7) pioneer work in the use of testosterone propionate in mammary carcinoma of mice, Nathanson and Andervont (11) using the androgen in larger doses, decreased the incidence of mammary tumors in a high tumor strain of mice. Ulrich (13) applied this form of therapy to humans and obtained a favorable response in two patients with inoperable mammary carcinoma. Loeser (10) treated five cases of recurrent carcinoma of the breast with large doses of androgen and noted improvement and no further recurrence for as long as five years. Fels (5) described three cases with good results in one and questionable results in the other two. Boger (3) reported one case treated with a combination of surgical castration and methyl testosterone orally, obtaining relief of pain and recalcification of osteolytic lesions. Adair and Herrmann (1) added eleven cases to the literature with favorable results in four. Farrow and Woodward (4) using smaller doses of androgen in a series of thirty-three patients obtained equivocal results. We wish to report five cases treated with testosterone propionate[2] in which results are sufficiently promising to warrant further investigation.

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[2] We wish to thank the Schering Corporation for the Oreton which was supplied us through the courtesy of Drs. Erwin Schwenk and W. H. Stoner.

CASE REPORTS

Case 1: M. H., a colored female, aged 46, was admitted to the Clinic in January, 1941. There was a history of a small boil developing about the right nipple while nursing her first child twenty-seven years previously. This drained spontaneously and in healing left a small mass. Two years before admission this mass began to increase slowly in size. She had had two normal pregnancies. At the time of admission she was menstruating regularly.

Physical examination disclosed a hard mass in the right breast seven centimeters in diameter, fixed to the skin, but movable over the chest wall. The nipple was retracted. The skin over the tumor was ulcerated. The axillary nodes were enlarged and very hard. No other metastases could be found by physical or x-ray examination.

The patient refused operation. Upon her return thirteen months later, the primary tumor had increased in size to eight by ten centimeters and ulcerated through the skin. The ipsilateral axillary nodes had also increased in size. The tumor was still movable over the chest wall, and no distant metastases were found. A radical mastectomy was performed at which time the tumor was found to encase the axillary structures and could not be completely removed. A month later a course of deep roentgen therapy was given to the right breast and axillary area. She was also given a sterilizing dose of roentgen therapy to the ovaries. Twenty-three months after surgery, two small recurrences were found adjacent to the operative scar. These responded to roentgen therapy but four months later recurrences reappeared in the same area, and in the axilla. No further treatment was instituted and in the following year she lost forty pounds in weight, developed pleurisy with a small amount of effusion in the left chest, and skeletal metastases to the left sixth rib, both ilia, right acetabulum and left ischium. She had vague gastrointestinal disturbances and an enlarged liver. There were many skin metastases around the operative site, some of which had ulcerated.

Forty months after operation and six years after the appearance of the primary tumor, she was extremely emaciated, and bedridden because of the severe pain in her right hip. Testosterone propionate therapy was instituted. She received 500 milligrams in a period of five weeks, given in 25 and 50 milligram doses intramuscularly. We attempted to give the injections at three day intervals, but this was not always possible. After receiving 250 milligrams there was marked improvement in symptoms of pain to the extent that the patient was able to be up and to make trips out of town. At this time she also complained of soreness in the metastatic areas. Roentgenograms two weeks after cessation of treatment showed no change in skeletal metastases despite alleviation of pain. These were repeated three months later and were reported as follows: "In the pelvis can be seen malignant metastases in both ilia lateral to the sacro-iliac joints, in the acetabular portion of the right ilium, in the right acetabulum, in the greater trochanter of the right femur, and in the body of the left ischium. There has been a definitely increased calcification in all but the focus in the acetabular portion of the right ilium and in the trochanter of the right femur. It appears as though the lesion in the left ilium is larger than it was in June, but there is a definitely increased density and a network of dense calcification. No new lesions are visible."

Subsequent roentgenograms continued to show recalcification of the metastatic lesions until seven months after cessation of her first course of testosterone. At this time there was a definite increase in size and amount of bone destruction of the osseous lesions. In the twelve months following her first course of treatment, she received 375 milligrams of testosterone propionate in 25 and 50 milligram doses at intervals which

were irregular because of our inability to control her appearance at the Clinic. She gradually became worse and when last seen was considered to be in the terminal stage of carcinomatosis with ascites.

Three months after cessation of her first course of testosterone, three control determinations of serum calcium were 11.8, 11.1, and 9.3 milligrams per cent. She was then given 125 milligrams of testosterone in two weeks, and her serum calcium on the day of the last injection was 15.3 milligrams per cent. Five months later, with no intervening treatment, the serum calcium was again 11.8 milligrams per cent. After another course of 150 milligrams of testosterone in six days, her serum calcium was 10.6 milligrams per cent on the second day after the last injection. In spite of the fluctuation of the serum calcium, inorganic phosphorus and alkaline phosphatase values determined simultaneously were normal at all times. Routine urinalyses showed no abnormalities. She had a persistent leucopenia, but no abnormalities in the differential count. The erythrocyte count was normal.

Case 2: B. N., a colored female, deaf mute, aged 36 was admitted to the Clinic in February, 1946. She gave a history of a mass in her left breast which had been growing rapidly for one year. She had had two normal pregnancies and was menstruating regularly at the time of admission.

Physical examination disclosed a hard irregular mass in the left breast six centimeters in diameter. It was not fixed either to the skin or chest wall. There were enlarged nodes, hard when palpated, in both axillae. A biopsy of the primary tumor and both axillary nodes showed carcinoma. There were no skeletal metastases. The hemogram and urinalysis were within normal limits.

Testosterone therapy was instituted, 25 milligrams was given intramuscularly for the first dose and then 50 milligrams every three days. Three weeks later she developed a generalized pruritus with some eczema formation. The dosage was reduced to 25 milligrams every three days and palliative topical applications were used on the skin lesions. There was no history of previous pruritus and no etiology could be found to explain it except perhaps the testosterone or its oil base. With continued therapy, however, it cleared up and then the dosage of androgen was increased to 100 milligrams per week given in 25, 25, and 50 milligram doses. Therapy was stopped empirically in 105 days after a total dosage of 1425 milligrams.

Reaction to the medication was nausea, flushing of the skin and possibly pruritus. She complained of "drawing" pain in her left breast and dull pain in legs and back, but these were not severe enough to incapacitate her. She developed an increased hirsutism of the lower extremities and diminution in size of the uninvolved breast. She menstruated three days before the onset of therapy and again six weeks later during therapy. There were no further menstrual periods until four weeks after cessation of treatment. Following this she was given a castration dose of roentgen irradiation.

Three to four months after treatment was stopped, her breasts began to increase in size but there was no change in the hirsutism. Her weight showed a small but definite increase at the beginning of treatment, maintained itself until therapy was stopped, and then gradually decreased (see Figure 1). The serum calcium was initially 12.4 milligrams per cent, and showed no significant change during the course of treatment. The alkaline phosphatase fluctuated between 1.6 and 6.0 Bodansky units and the serum inorganic phosphorus between 2.75 and 5.10 milligrams per cent. No abnormal changes in the hemograms and urinalyses were noted.

In the eight months prior to castration, there had been a definite increase in the size

of the primary tumor with fixation to the skin in the anterior axillary fold. The regional axillary metastases also increased in size but no discernible distant metastases developed. No systemic or symptomatic changes in the patient have been noted.

Case 3: F. D., a white female, aged 55, was admitted to the Clinic in March, 1946. She gave a history of a hard mass which had been present in the right breast for several years. Four months prior to admission she noticed two small "knots" which seemed to be attached to the mass and to the skin. These soon broke down and discharged a thick yellowish material. She believed she had lost 30 to 35 pounds during the previous year.

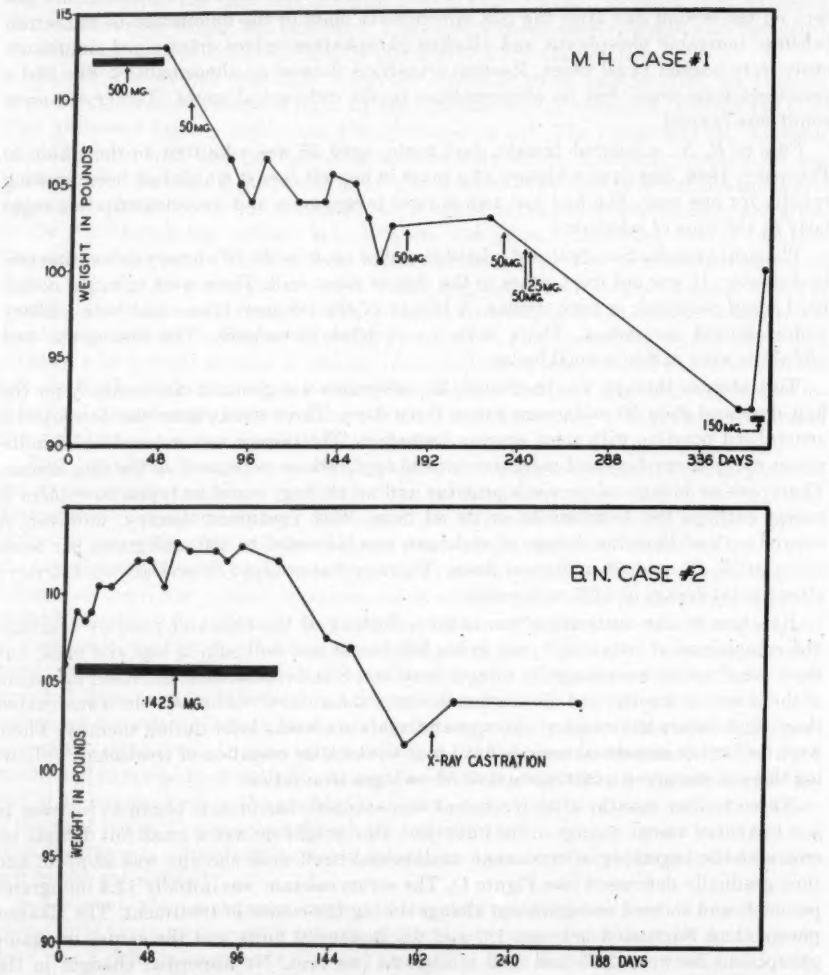

FIG. 1. Graphic representation of the effect of testosterone propionate (Oreton) on the weight of patients treated for carcinoma of the breast.

Physical examination revealed the entire right breast to be replaced by carcinoma measuring about 13 by 8 centimeters. The tumor was firmly fixed to the chest wall and had invaded the overlying skin forming an ulceration five centimeters in diameter. There was a separate stony-hard mass above the breast fixed to the chest wall just to the right of the angle of Lewis. The right axillary nodes were enlarged and hard. Biopsy of the ulcerated area revealed carcinoma. Roentgenograms showed metastases to the lungs and a sclerosing lesion of both sacro-iliac joints. An incidental finding was a nodular non-toxic goiter which had been present for twelve years.

She received 550 milligrams of testosterone propionate in 25 and 50 milligram doses over a period of 75 days. No improvement was noted in the primary tumor or the metastases and she became progressively weaker. Because of this and the fungating nature of the lesion, palliative roentgen therapy was given to the primary lesion. The patient did not improve and died at home seven months after she was first seen. Permission for autopsy was not obtained.

No reactions to the androgen were noted, nor any effect on the hemogram, serum calcium, inorganic phosphorus, or alkaline phosphatase. Her goiter did decrease in size during treatment.

Case 4: D. W., a white female, aged 42, was admitted to the Clinic in February, 1945. She had first noticed a small lump in her left breast fifteen months prior to admission. Two months after the appearance of the first lesion, a small mass appeared in the skin of the right lumbar region. At this time a left simple mastectomy and removal of the skin nodule was done at another hospital. Both lesions were diagnosed as carcinoma. Her post-operative course was uneventful for the first five months, when she developed pain in the left axilla and both sides of the neck. A radical dissection was then done on the left axilla at another hospital. Following the operation she had pain in her neck and left arm, which at the time of her admission to our Clinic was so severe that she could not move these parts and was confined to bed.

Physical examination revealed skin metastases along the healed operative scar. The supraclavicular and cervical lymph nodes bilaterally were matted together in almost solid sheets, forming a continuous mass of firm tissue extending from the supraclavicular fossa to the tip of the mastoid on both sides. The skin over these areas was edematous and thickened. The left arm was edematous with marked tenderness on pressure over the middle third. The axillary nodes were involved bilaterally. The right breast contained no tumor. There was a single metastasis recurrent in a small scar in the right lumbar region. Roentgenograms of the skeleton were suggestive of a destructive process in the head of the left humerus. Hemograms, urinalysis and blood chemistry studies revealed nothing of significance.

She was admitted to the hospital and given 25 milligrams of testosterone propionate daily for a total of 300 milligrams. Fifty milligrams three times weekly was then prescribed and she was sent home. A total of 750 milligrams of testosterone was administered in 35 days. There resulted a very noticeable improvement of the pain in her neck and left shoulder but she continued to get worse and died 110 days after the onset of therapy. She frequently complained of sudden swelling and fullness in the posterior triangles of her neck occurring from 12 to 24 hours after the administration of the 50 milligrams of testosterone. The attending nurse stated that at these times an increased edema of the neck was visible. This would subside in about 12 hours. We have no explanation for this phenomenon. An autopsy was obtained and the diagnosis was recurrent carcinoma of the left breast with metastases to both axillae, right breast, cervical lymph nodes bilaterally, mediastinal lymph nodes and liver, and bronchopneumonia. Micro-

scopic study did not reveal any changes in the malignant cells which we could attribute to the hormonal therapy. However, she had not received testosterone for two months before death.

Case 5: C. K., a colored female, aged 45, was admitted to the Clinic in April, 1946. She had had a "knot" present in her left breast for twenty months. The tumor increased in size and three months before admission her right shoulder became painful.

Physical examination revealed an acutely ill, cachectic patient, obviously in pain. Any movement of her head, trunk or extremities elicited severe but vaguely localized pain. Movement or pressure of the upper end of the right humerus invoked excruciating pain. A satisfactory physical examination and roentgen study were impossible. In the left breast was a stony-hard mass six centimeters in diameter fixed to the skin but not to the underlying structures. The left axillary nodes were enlarged, hard and matted together. She presented the picture of terminal carcinomatosis.

The hemogram and urinalysis were not unusual. The serum calcium was 14.6 milligrams per cent, the alkaline phosphatase was 1.8 Bodansky units. She was given 175 milligrams of testosterone propionate in a period of four days. The pain in the right shoulder improved to the extent that she could voluntarily move her right arm which heretofore she had been unable to do. She became moribund on the sixth hospital day and died on the eighth day. An autopsy was performed and the diagnosis was carcinoma of the left breast with metastases to the left axillary lymph nodes, head of the right humerus, liver, lungs and occipital bone with complete destruction of the bone and extension into the cerebellum, bilateral pulmonary edema, healed tuberculosis of the lungs and right axillary nodes, fibrous pulmonary adhesions, fibrous peritoneal adhesions, and leiomyomata uteri. Microscopically, we were unable to find any change in the malignant cells which we could ascribe to the hormonal therapy.

COMMENT

All the above cases were treated with testosterone propionate in sesame oil (Oreton) by intramuscular injections. It was given in doses of 25 and 50 milligrams per injection for a total dosage of from 175 milligrams in four days to 1425 milligrams in 105 days. We tried to maintain the weekly dosage between 75 and 100 milligrams but this was not always possible as several of the patients lived at some distance from the Clinic.

The most encouraging aspect of this work is the effect of the male sex hormone on the pain and disability of the patient. This was markedly demonstrated in three of our five cases, of which cases one and four are noteworthy. The former was bed-ridden because of severe leg pain due to extensive bony metastases. After the first week of therapy she became ambulatory and several weeks later felt well enough to travel. The latter patient was taking narcotics to relieve pain in her neck and shoulders which was severe enough to confine her to bed. After three weeks of therapy she was able to do without the narcotics and to get out of bed although she did not become completely ambulatory. In case five, in spite of the brief period of therapy and her terminal condition, relief of pain was sufficient to allow movement of the upper extremities the day before death. This she had been unable to do when admitted to the hospital. Although it is difficult

to evaluate, it is our impression that there was a definite improvement in appetite and sense of well being in three of the five patients. This relief from pain, especially that due to skeletal metastases, has been observed by others. Farrow and Woodward (4) mention relief from pain in about one half of thirty-three patients, although there was no evidence of control of the disease. Fels (5) described alleviation of pain in two patients. The results in one were quite dramatic, the patient becoming ambulatory after being bed-ridden for eighteen months because of pain. Adair and Herrmann (1) likewise obtained relief from pain in three patients. Boger (3) reported similar results in one patient treated with surgical castration and oral androgen.

Weight increase occurred in two of our patients, cases one and two. We found a direct correlation between the patient's weight and the administration of androgen. One maintained her weight and the other showed an increase during the course of therapy. Upon withdrawal of the androgen, both patients showed a definite progressive loss of weight. This is depicted in Figure 1. Loeser (10) reported a case in which there was improved health and a gain of five pounds. The improvement lasted four months after cessation of testosterone therapy, and then the weight began to decline. Adair and Herrmann (1) observed weight gains in three of four patients receiving large doses of testosterone. Their patients gained as much as fifteen pounds in eight weeks. Since loss of weight is a poor prognostic sign in patients with carcinoma, the weight gains observed with the use of testosterone propionate are encouraging. We recognize the possibility that the weight gain may be a direct effect of the androgen rather than a result of an inhibition of malignant processes.

The serum calcium, inorganic phosphorus, and acid and alkaline phosphatases[3] were followed in three of the patients. One of these, case one, had numerous skeletal metastases. She received 500 milligrams of testosterone propionate in a six weeks period. Ninety days after cessation of therapy, calcification of the osteolytic skeletal metastases was demonstrable by roentgenogram. Following this her therapy was sporadic and inadequate (she was reluctant to return to the Clinic) and the bone destruction increased. Her serum calcium during this period fluctuated between 9.3 and 15.3 milligrams per cent. At one time after receiving two 50 milligram doses of testosterone ten days apart, the calcium rose to 15.3 milligrams per cent. The subsequent determination five months later was 11.8 milligrams per cent. Serum alkaline phosphatase levels, which were determined coincidentally with the calcium, were within normal limits. These results are

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[3] We wish to express our appreciation to Dr. Carroll F. Shukers, Department of Biochemistry, for performing the serum phosphatase determinations.

compatible in part with those reported by Farrow and Woodward (3). They found that the serum calcium of patients with carcinoma of the breast and skeletal metastases fluctuates spontaneously. They treated thirty-three patients with a maximum total dose of 300 milligrams of testosterone, and three patients with larger doses of testosterone plus estrone. These patients showed an increased activity of the bony metastases. Adair and Herrmann (1) found improvement and calcification of osseous lesions in three of their cases, two of which had a concomitant rise in the serum alkaline phosphatase. They used massive doses of testosterone propionate, with a total dose of about 4000 milligrams. Our patient showed improvement at first on regulated therapy, and then regression when therapy became irregular and inadequate. The observations of Farrow and Woodward, Adair and Herrmann, and ourselves would suggest that small or inadequate doses of androgen tend to activate skeletal metastases, while larger doses over a relatively short period are beneficial. The two cases without skeletal involvement showed no abnormality in the serum calcium, phosphorus or phosphatases.

The effect of testosterone on the primary breast tumor and soft tissue metastases is discouraging with the dosage we have used. Case three received 550 milligrams in 105 days with no detectable changes. The ulcer became cleaner and lost much of its odor, but this could well have been due to the topical therapy administered. In case two the primary tumor definitely increased about three times in size and became more fixed to both skin and anterior chest wall. This was after a total administration of 1425 milligrams of testosterone in 105 days. Adair and Herrmann (1) had one case of almost complete regression of the primary tumor and axillary metastases with a dosage of 3975 milligrams over a 105 day period. Therefore the lack of response in our case may have been the result of too small a dosage. Two of our patients, cases one and four, had superficial soft tissue metastases; in one case to the skin of the chest wall, and in the other to the supraclavicular and cervical lymph nodes. Our treatment here also failed to elicit a favorable response. The skin metastases in case one actually increased in number although the skeletal metastases showed improvement. A very interesting phenomenon was observed in case four which we cannot explain. This patient complained on several occasions of a transient feeling of fullness and swelling in the region involved by the cervical metastases. This occurred about twelve to twenty-four hours following each of several injections of testosterone and seemed to be definitely correlated with it. Our knowledge of the effect of testosterone on tumor cells is still too incomplete to offer an explanation.

We encountered no serious toxic reactions with testosterone propionate in sesame oil (Oreton). Most of the patients had the expected vaso-dilata-

tion. Although one patient had a generalized pruritus during therapy, this subsided spontaneously without stopping treatment. We cannot definitely ascribe this condition to the effects of the hormone. Amenorrhea occurred in the one patient who was menstruating prior to treatment. This was temporary and menses occurred four weeks after the cessation of treatment. Hirsutism and flattening of the non-cancerous breast occurred in this same patient who had received 1425 milligrams of testosterone propionate. This was the only patient who showed evidence of virilism.

There were no effects of the androgen on the hemograms, urinalyses, and serum proteins in any of these patients. One patient had a leukopenia when therapy was instituted, but this remained unchanged both during and after treatment.

Our results in this study are sufficiently encouraging to us to warrant our continuation of this method of treatment of inoperable carcinoma of the breast.

CONCLUSIONS

1. Five patients with carcinoma of the breast and metastases to the soft tissues and skeleton were treated with testosterone propionate.
2. Following therapy symptomatic relief of pain and increased sense of well being of the patients were pronounced.
3. Moderate doses of testosterone propionate have no beneficial effect on the primary tumor or soft tissue metastases.
4. The results suggest that recalcification of osteolytic metastases occurs with adequate therapy.
5. No serious side reactions were noticed with this method of treatment.

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SYMMETRIC CEREBRAL CALCIFICATION WHICH FOLLOWED POSTOPERATIVE PARATHYROID INSUFFICIENCY: REPORT OF A CASE

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THREE communications pertaining to symmetric cerebral calcification were published by Camp, Love, Eaton and Haines (2, 3, 5) in 1938 and 1939, and a thesis on this subject was prepared by one of us (Eaton (1)). In these communications were described some of the roentgenographic (Fig. 1*a* and *b*) observations in seven cases and the data obtained at necropsy in one of these cases.

The point was emphasized that symmetric cerebral calcification was often associated with spontaneous parathyroid insufficiency, and it was our opinion that the changes in the brain resulted from parathyroid insufficiency. This hypothesis could, of course, be somewhat strengthened by the finding of symmetric cerebral calcification in a case of postoperative parathyroid insufficiency, but this we had been unable to do at the time of our last publication. Failure to find such an occurrence may have been due in part to failure in earlier years to make roentgenograms of the skull in our cases in which parathyroid insufficiency followed thyroidectomy, and in part, also, to the fact that whereas the condition of most patients who have postoperative parathyroid insufficiency is properly diagnosed and treated early, many patients with spontaneous parathyroid insufficiency are untreated for many years. It is generally true also that, in most cases, spontaneous parathyroid insufficiency is of severe degree, whereas a larger number of those patients who acquire the deficiency after operation have it to a less severe degree.

In 1939, Kahn, Lion and Zimmerman (4) reported a case in which cerebral cortical calcification simulated Pick's disease. The disease occurred in a patient who had postoperative parathyroid insufficiency, and study of tissue removed from the brain showed the same type of change that we had found in the brain of one of our patients. In this case the chronic parathyroid insufficiency appeared to have been present for fourteen years. The authors have discussed the possibility that the cerebral calcification might be due to parathyroid insufficiency.

The occurrence of calcification in patients who have parathyroid insufficiency has been further corroborated by the finding of roentgenographic

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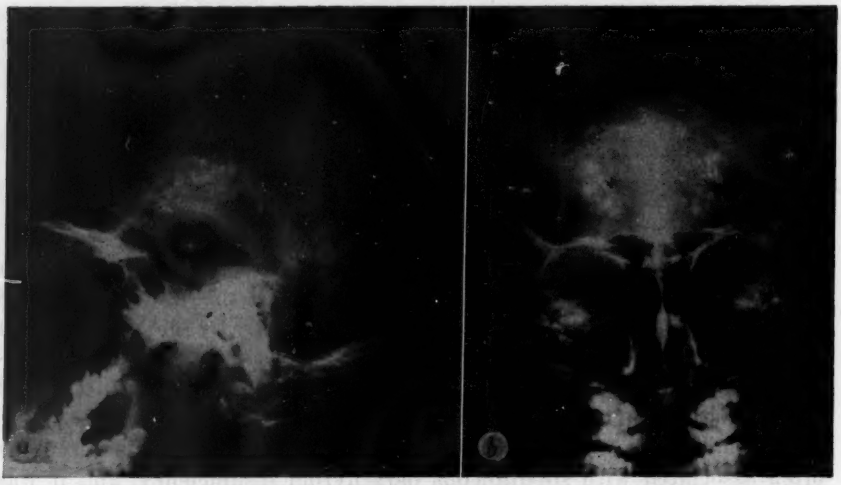

FIG. 1*a*. Left lateral view of the skull of a boy thirteen years and seven months old, with spontaneous parathyroid insufficiency showing areas of calcification below the usual situation of the anterior horn; *b*, anteroposterior view of the skull of the same patient, showing symmetric areas of calcification in the region of the basal ganglia.

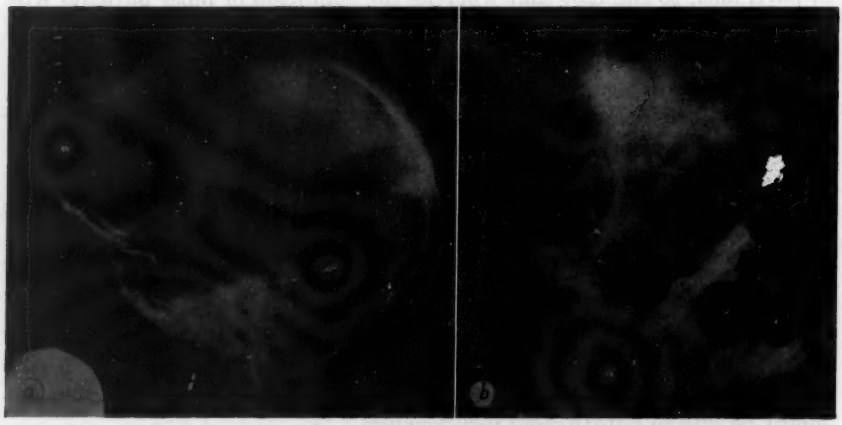

FIG. 2*a*. Left lateral aspect of the skull of the patient in the case reported in this paper, showing extensive calcification of the basal ganglia, and slight calcification of the cerebral hemisphere above the basal ganglia; *b*, anteroposterior view of the skull of the same patient, showing symmetric distribution of the calcification.

evidence of cerebral calcification in 11 of 17 patients with spontaneous parathyroid insufficiency studied at the Mayo Clinic from 1935 through 1945 and by the finding, in one of these 17 cases, of calcification in an area of the subcutaneous tissue.

The present report deals with a patient who had postoperative parathyroid insufficiency and who also had symmetric cerebral calcification.

REPORT OF A CASE

A factory worker forty-two years old entered the Mayo Clinic on January 1, 1944, complaining of poor vision and frontal headache. Eighteen months prior to admission, he first noted difficulty with his vision. New glasses had been fitted; they had maintained improved vision for about a year. At the end of that period blurring of vision had become progressively worse.

When we saw the patient he had been suffering for about two months from persistent dull frontal headache and occasional sharp, shooting pains over both temples. There were also sharp frontal pains which might occur at any time of the day or night. Pains in the head did not become worse during coughing, sneezing or bending, but diplopia occurred frequently. An anodyne (anacin) gave relief. The patient's wife stated that he was becoming much more irritable, fidgety and childlike, and that his memory had deteriorated markedly. The possibility of his having a brain tumor had been considered.

The history of this patient revealed a chronically nervous disposition that had become worse during the previous ten years. He had had a goiter and had complained of dyspnea in 1920. Thyroidectomy had been performed. On the morning after thyroidectomy he had experienced carpopedal spasm, with recurrent attacks at three months and twelve months postoperatively. The patient then had been free from such attacks for eighteen years, although he said he occasionally felt "dizzy and lightheaded."

In 1940, he had experienced a fourth attack of carpopedal spasm, followed by several attacks which had occurred about every other day. One episode had awakened him from sleep, and he had noted that he usually slept for several hours after an attack. He had never bitten his tongue or become incontinent during an attack. There was no family history of convulsions. His only aura consisted of a sensation of dizziness before attacks; he rejected the possibility of hyperventilation. The last episode of carpopedal spasm had occurred in April, 1943, about eight months before the patient came to the clinic. The patient drank much milk, and stated that he thought food relieved his nervousness.

Examination disclosed a well-developed, well-nourished white man who exhibited an occasional muscle tremor. Blood pressure was 115 systolic, and 70 diastolic, expressed in millimeters of mercury. The pulse rate was 66. Residual thyroid tissue, palpable on the left, was estimated to be about 2.5 by 5 cm. A presystolic murmur could be heard at the apex cordis, and there was a diastolic murmur at the pulmonic area. Reflexes were moderately diminished bilaterally. Chvostek's sign was elicited, and Trousseau's sign was pronounced. The ocular fundi appeared to be normal, so far as they could be seen, but diffuse opacity of the lenses of both eyes was noted. Results of the urinalysis, of the Kline test of the serum, and of roentgenograms of the thorax were negative. Results of blood counts and of electrocardiography were within normal limits. The basal metabolic rate was −4 per cent. Roentgenograms of the skull were reported as demonstrating "very extensive calcification of the basal ganglia on both sides, especially on the right. There is some slight calcification in both cerebral hemispheres above the basal ganglia" (Fig. 2*a* and *b*).

The value for serum calcium was 5.5, and that for phosphorus, 6.6 mg., per 100 cc. of serum. Two grams of calcium lactate in solution was administered in doses of one teaspoonful (about 4 cc.) four times daily, along with two capsules (1.25 mg.) of dihydrotachysterol, for two days; then one capsule (0.625 mg.) of dihydrotachysterol was administered daily. Cataract surgery was deferred for several months.

The patient returned to the clinic on March 12, 1945, for removal of cataracts. His sight had become progressively worse, so that he had been unable to work, but he was much less nervous than formerly, and had not had convulsions or numbness and tingling of the hands since the institution of adequate therapy. He had continued to take one teaspoonful of calcium lactate three times daily, but had not continued to take dihydrotachysterol. He had gained 5 pounds (about 2 kg.) during the two months prior to this second visit to the clinic.

Results of examination were as previously noted except that Chvostek's and Trousseau's signs were not obtained. Studies of serum chemistry at this time showed the value for calcium to be 9.0, and that for phosphorus to be 5.4 mg., per 100 cc. of serum. The patient underwent operation on March 19, 1945, at which time an immature cataract was removed from the right eye. Recovery was without incident.

COMMENT

This case, illustrating the occurrence of symmetric cerebral calcification in a patient who had parathyroid insufficiency which apparently developed after thyroidectomy, seems to us to support the opinion that the characteristic cerebral pathologic process actually is secondary to parathyroid insufficiency. The intermittency of symptoms in this instance is similar to that seen frequently in cases of postoperative parathyroid insufficiency. The control of symptoms, including convulsions, without demonstrable changes in the roentgenologic picture of cerebral calcification, is also similar to the observation in other patients. In fact, in one of our patients (Fig. 1*a* and *b*) with spontaneous parathyroid insufficiency—a boy thirteen years and seven months old who had had convulsions for six years—continuous treatment resulted in control of convulsions and was accompanied by a rise in the intelligence quotient from 73 to 99, although the cerebral calcification showed no change over a period of nine years. Similar experiences have been noted in other patients.

SUMMARY AND CONCLUSIONS

Symmetric cerebral calcification, demonstrable roentgenographically, frequently is observed in the presence of idiopathic parathyroid insufficiency, and is herein reported in a case in which parathyroid insufficiency followed thyroidectomy. This case supports the opinion that the cerebral changes are secondary to the metabolic disturbance resulting from insufficient parathyroid secretion, and that these cerebral changes are not the cause of the disturbance. Adequate treatment of parathyroid insufficiency leads to relief of clinical symptoms, but does not cause the cerebral calcification to disappear.

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FEMINIZING TUMOR OF THE TESTIS

Presumably Aberrant Adrenocortical Tumor

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IN MOST instances of feminizing tumors observed in adult males, the most conspicuous symptom of feminization is gynecomastia, accompanied by more or less pronounced genital atrophy and sometimes but not always, loss of capacity for sexual function. The appearance of gynecomastia may also be due to other causes, however. Thus the phenomenon has been described as a hereditary familial character (5). In lesions producing atrophy of the testis, or after castration, gynecomastia or gynecomastia-like deposits of fat may appear even though this is far from being the rule (15).

The tumors which in adult males have given rise to feminization have originated from the adrenal cortex or testis. The feminizing adrenocortical tumors have most often been carcinomas, but on the whole they are rare. In 1942 Roholm & Teilum (17) described such a case, reviewing at the same time the 6 instances of feminizing adrenocortical tumors previously reported.

When adrenocortical tumors are able to alter the sex characteristics usually in the male direction, the change is due to production or, rather, hyperproduction of androgens or estrogens respectively. Whenever testicular tumors have been feminizing, physical changes have also been due to hormonal production. At any rate this applies to the highly malignant chorionepithelioma of the testis—the testicular tumor which most often gives rise to gynecomastia. Aside from chorionepithelioma, gynecomastia has been observed in a few cases of other malignant testicular tumors—as in seminoma (21, 8) and embryonal carcinoma (8). In such cases of malignant testicular tumor it is difficult to establish the genesis of the gynecomastia, which perhaps may be due to the prevention of the testicular function by the tumor rather than to any endocrine function of the tumor itself.

Finally, gynecomastia has been observed a few times in cases of nonmalignant testicular tumors; in two cases of interstitial cell tumor (14, 10) and in one case of testicular paraganglioma. These cases will be mentioned further in the discussion of the following instance of feminizing testicular tumor observed by the writer.

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* Surgeon-in-chief: C. D. Bartels.

CASE HISTORY

The patient was a farmhand, 28 years old, who was admitted to the hospital in March 1942. In the last couple of years he had noticed that the mammae were increasing in size and he entered the hospital to be treated for this anomaly.

There had been no pain or unusual sensation in the mammae, nor any secretion. He does not remember anything about previous traumatic injury to, or pain in the scrotal region, and he had not noticed any enlargement of the left testis. Libido and sexual potency were said to be normal.

He was of medium height, of virile build with well-developed muscles and no excess

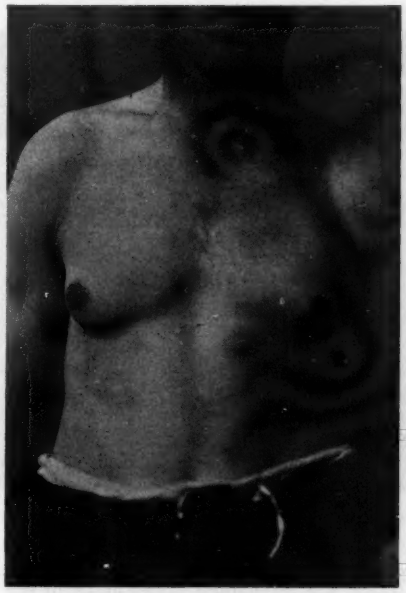

FIG. 1

adipose tissue. His hairiness was of the masculine type. The mammae were rounded as in a young girl, with distinctly well-developed mammary glands. No secretion could be expressed from the papilla (Fig. 1). An examination of the genitals showed the pubes to be normal and the penis normally developed. Both testes were in the scrotum but the right was somewhat atrophic, about the size of a pigeon egg. The left testis was about twice as large, and at its upper pole a well-defined tumor was palpable.

Surgical intervention by semicastration was performed on March 20. The removed testis contained a well-defined tumor, about the size of a large hazel-nut, arising from the testicular hilus; on section, the cut surface was yellowish-orange in color.

Histological Description (Dr. Fr. Gregersen): The testis showed the presence of a roundish tumor that had no connection with the tubules and no relation whatever to the testicular parenchyma, being surrounded by a capsule of connective tissue. The tumor was lobated by rather coarse streaks of connective tissue; it was very rich in cells, being

made up of rather large cells, arranged in alveolar heaps or in narrow streaks, here and there in rosette-like pattern, surrounded by capillaries and sinusoids, and in some areas by delicate connective tissue septa. The cells were rather rich in protoplasm, varying in form from plump spindle-formed to more cylindrical, somewhat epithelioid cells, often adjusted in form to each other. In sections stained after v. Giesen-Hansen the cells were smoky-yellowish in color. The nuclei were rather large, round or slightly ovoid, with a single nucleolus. The tumor tissue had nothing in common with tumors arising from testicular parenchyma, and there was nothing suggestive of ovarian tissue. As the specimen was fixed in formalin-alcohol, it was not possible to judge whether it might have been chromaffin. An attempt at impregnation with silver showed the cytoplasm to be

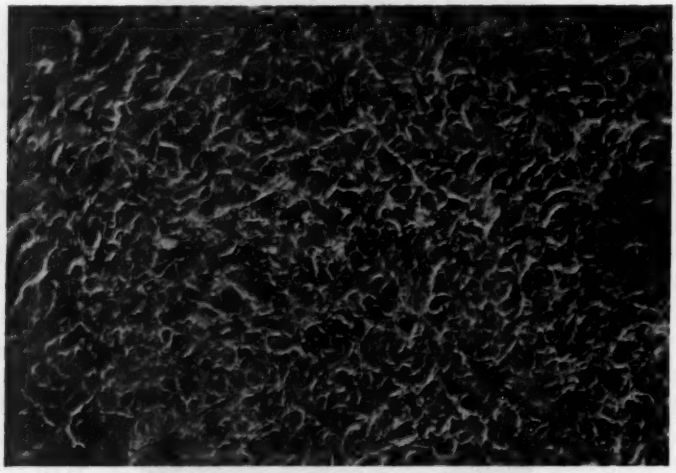

FIG. 2

coarsely granular, but there was no definite argyrophilia of the granules. Nor did the Giemsa stain give any absolutely certain color reaction, as the cells became bluish-green, not markedly green. Mitotic figures were rather numerous. According to the structure of the tumor, and the character and arrangement of the cells, it resembled a tumor arising from chromaffin tissue. Owing to the fixation of the specimen in formalin-alcohol, however, it was not possible to establish this diagnosis with certainty.

The tumor was well-defined and showed no destructive growth, so that it afforded no histological evidence of the malignancy which might have been suspected because of the unusually large number of cells and many mitoses. (Fig. 2).

Hormonal Analysis (Dr. Christian Hamburger), on March 12 (prior to the removal of the tumor): Friedman reaction negative.

Gonadotropin: 0 (*i.e.*, <50 M.U. per day).

Estrogens: about 200 M.U. per day.

Androgens: 25 I.U. per day.

On April 7 (after removal of the tumor):

Gonadotropin: about 50 M.U. per day.

Estrogens: about 50 M.U. per day.

Androgens: about 62 I.U. per day.

At the time of the patient's discharge from the hospital, about 3 weeks after the operation, the breasts had not diminished distinctly in size. The patient has been re-examined several times, most recently in April 1944. During this period the breasts have decreased gradually until they are now only slightly enlarged. Remnants of the previously enlarged mammary glands are still palpable. The patient is very satisfied with the result. The right testis has grown distinctly, being now of normal size and consistency. There has been no disturbance in sexual potency. In the meantime the patient has married and is now the father of a child. He feels perfectly well. There are no signs of metastasis from the removed testicular tumor.

DISCUSSION

There can be no doubt that the testicular tumor in this case was feminizing. This is indicated by the fact that the gynecomastia appeared together with the development of the tumor and disappeared after the removal of the tumor. This is further indicated by the demonstration of increased estrin excretion prior to the removal of the tumor and normal estrin excretion after the operation, as well as by the previous atrophy of the right testis and its subsequent growth after the operation. There was no disturbance of the sexual potency, it is true, but this feature was also absent in several of the cases mentioned in the literature.

In trying to classify the present tumor among the feminizing testicular tumors mentioned in the introduction, the possibility of chorionepithelioma can be excluded at once because of the morphology of the tumor, the course of the case and the absence of excretion of chorionic gonadotropin with the urine. Nor has this tumor anything in common with seminoma or embryonal carcinoma. On the other hand, the tumors arising from interstitial cells in the testis are rather to be taken into consideration. According to the prevailing view, the interstitial cells (Leydig's cells) in the testis produce a masculine hormone. In keeping with this view pubertas praecox has been observed in the cases of boys in whom interstitial cell tumors have been described (19, 22). In those cases—nearly 20—in which interstitial cell tumors have been described in adult males, changes in the sexual characteristics were observed only in the two reported by Monaschkin (14) and Hunt and Budd (10), where the tumor was accompanied by development of gynecomastia and, in the case of Hunt and Budd, also with disturbances in sexual potency.

The interpretation of these two cases, however, is open to criticism. Thus Mathias (9) thinks that in Monaschkin's case the lesion involves an inflammatory reaction resulting in an increase in interstitial cells, not any true tumor formation. This patient presented a distinct atrophy of the other testis, aspermia and feminine limitation of the pubes, on which account Mathias thinks that the patient was a castrate-like, slightly feminine

male with gynecomastia that could not have been produced by increase in interstitial cells.

In Hunt and Budd's patient, a man of 42 years, the feminizing testicular tumor was well-defined, 2–2.5 cm. in diameter, situated in the mediastinum of the testis, yellowish on the cut surface, and morphologically the tumor cells resembled interstitial cells. The urine showed an excretion of 1000 units of luteinizing gonadotropin (chorionic gonadotropin?) per liter. The excretion of estrogen and androgen was not examined. The increased excretion of luteinizing gonadotropin is difficult to understand in connection with an interstitial cell tumor; it rather suggests that the tumor or the removed testis contained chorionic elements. But this assumption is not corroborated by the course of the case, as no recurrence or metastasis was observed during a period of two years. Thus it seems rather doubtful that these two feminizing testicular tumors really were interstitial cell tumors.

In its course, as well as in the size, location and macroscopic appearance of the tumor, our case resembles the case reported by Hunt and Budd. Microscopically, however, the tumor cells in our case differ somewhat from interstitial cells, being darker in color, deficient in protoplasm and more closely packed. So this could hardly have been an instance of interstitial cell tumor.

From the histological description it is evident that in its structure and cellular morphology this tumor is like those arising from the chromaffin tissue in the adrenal medulla or from the paraganglia. In the literature, an instance of gynecomastia has been described in connection with a testicular tumor reported by Botteselle as a paraganglioma.

It seems rather strange, however, and it has not been described before, that a tumor consisting of adrenomedullary cells should be able to alter the sex characteristics whereas this phenomenon has been reported not infrequently in adrenocortical tumors. So the question is if it might not be more likely in our case (and perhaps in that of Botteselle too) that the tumor was an aberrant adrenocortical one rather than a paraganglioma of adrenomedullary cells. At any rate in our case it was not possible to prove that the cells belonged to the chromaffin system, and from the only description of Botteselle's case accessible to the writer it is not evident that the tumor described as a paraganglioma was chromaffin. In these cases it would hardly be possible from the cellular morphology alone to decide with certainty whether the tumor was made up of adrenocortical or adrenomedullary cells; and it happens but seldom that an adrenocortical tumor presents the three zones of cells typical of the adrenal cortex. Morphologically, the cells in our case may very well be adrenocortical cells. From the description and the microphoto it will be noticed that in our case

the cells are arranged in alveolar heaps, narrow streaks, sometimes forming rosettes, surrounding capillaries and sinusoids, or surrounded by such vessels—a microscopic picture that corresponds very well to the features encountered in tumors of the adrenal cortex. Also the increased output of estrin and the lack of gonadotropin excretion correspond to findings that may be expected in a feminizing tumor of the adrenal cortex.

It may perhaps seem rather surprising that a tumor of the testis should consist of adrenocortical cells. Still, from the pathological anatomy we know that adrenocortical tissue may occur in other parts of the organism besides the adrenal. Small accessory adrenals have been demonstrated not only in the immediate vicinity of the adrenal but also along the course of the internal spermatic vein (2) and in the ligamentum latum, near its lateral margin, where the occurrence of these bodies was first demonstrated by Marchand (11), on which account they often are designated as adrenals of Marchand. Marchand (1882) described then a small yellowish body, 1–3 mm. in diameter, built up histologically as adrenocortical tissue. Later, such bodies have been demonstrated also between the testis and epididymis (3), in the mediastinum of the testis (18), in the vicinity of the epididymis (23) and the ductus deferens (20, 13). They are found fairly often in the newborn and infants, but have been demonstrated also in adults. As a rule, they are quite small, only a few millimeters in diameter but in rare instances they have attained cherry size. In certain cases these accessory adrenals have been looked upon as the origin of tumor formation (16).

In a very few cases, changes in the sexual characteristics have been described in connection with such aberrant adrenocortical tumors located in the ligamentum latum (12, 7, 6, 4). As far as the writer has been able to find out, hitherto no instance has been described of a feminizing adrenocortical tumor localized to the testis. As mentioned, however, several things suggest that the tumor here described constitutes such a case, perhaps developing from a Marchand adrenal located in the hilus of the testis.

Nearly all the feminizing adrenocortical tumors reported previously (17) have been malignant. On account of its richness in cells and the rather numerous mitoses, the tumor here described is a little suspect of malignancy. Possibly these characters of the present tumor are the reason why it produced estrogen and brought about the change in the sexual characteristics in contrast to most other aberrant adrenals or instances of hyperplasia or tumor formation developing from such bodies. In the present case, however, there was no definite histological evidence of malignancy of the tumor and the course of the case under two years observation without any recurrence or metastasis, excludes the probability of malignancy.

SUMMARY

Reference is made to the various feminizing tumors, and an account is given of their mode of action.

The feminizing testicular tumor observed by the writer was found in a man of 28, in whom gynecomastia had developed in a couple of years. In addition there was atrophy of the non-tumor-bearing testis, increased excretion of estrogen with the urine, but no output of gonadotropin and no disturbance of sexual potency. After removal of the tumor, the estrogen output decreased to normal, the gynecomastia subsided almost completely within two years, and the other testis increased to normal size. The tumor removed was a little larger than a hazel-nut, well-defined, localized to the hilus of the testis. On the section surface it was yellowish-orange in color. Histologically it showed no resemblance to any of the tumors usually occurring in the testis.

As to the nature of the tumor, the author discusses the more obvious possibilities of interstitial-cell tumor, paraganglioma and adrenal cortical tumor. On the basis of the histological features and the endocrine function of the tumor, the author arrived at the conclusion that presumably it was an aberrant adrenal cortical tumor, developed from accessory adrenal cortical tissue located in the hilus of the testis.

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THE ASSOCIATION

FOR THE STUDY OF

INTERNAL SECRETIONS

TWENTY-NINTH ANNUAL MEETING

FRIDAY AND SATURDAY, JUNE 6–7, 1947

Haddon Hall, Atlantic City, New Jersey

ABSTRACTS OF PAPERS PRESENTED

ABSTRACTS ARRANGED ACCORDING TO NUMBER

Friday, June 6

9:30 A.M. *Viking room*

1. STUDIES IN CORPUS LUTEUM FUNCTION.

J. S. L. Browne, J. S. Henry and E. H. Venning. (From the McGill University Clinic, Royal Victoria Hospital, Montreal, Canada, and the Department of Obstetrics and Gynecology, McGill University.)

Sodium pregnanediol glucuronidate was determined by the method of Venning and correlated with endometrial biopsies. In 21 cycles in 20 cases biopsies showed no progestational changes when taken just before the onset of the menstrual period, and, the pregnanediol in the same cycle was absent. In 45 cycles in 36 cases the biopsies showed early or late progestational changes and this was well correlated with the time of onset or the presence of pregnanediol. On no occasion was the pregnanediol positive in a cycle in which the biopsy showed no progestational change. There were no cases of adrenal tumours with amenorrhoea in this series; in such cases pregnanediol has been found to be positive with an atrophic endometrium. On 10 cycles in 8 cases the biopsies showed progestational changes but no pregnanediol was present in the same cycle. Some of these discrepancies are explicable on the grounds of very large volumes of urine which prevented the detection of pregnanediol. The effect of chorionic gonadotropin on pregnanediol excretion has been further studied. If chorionic gonadotropin is administered in a dose of 1000 international units daily in the early part of the luteal phase, in some instances a marked increase in the excretion of estrogen occurs (up to as high as 3,800 units in one case). The excretion of pregnanediol is prolonged and endometrial biopsies show histological changes similar to those seen in early pregnancy. In certain cases however, the corpus luteum function cannot be prolonged by the administration of this dose.

2. PROGESTERONE THERAPY OF UTERINE FIBROMYOMATA.

Albert Segaloff, John C. Weed (by invitation) and William Parson. From The Alton Ochsner Medical Foundation, The Ochsner Clinic and the Departments of Medicine and Gynecology, Tulane University of Louisiana School of Medicine, New Orleans, Louisiana.

Patients with uterine fibromyomata have been treated with progesterone.

Only those patients in whom it has been possible to outline the tumor by roentgenography with either intraperitoneal carbon dioxide or the intrauterine instillation of radiopaque oil have been followed.

Three patients were treated for 39 to 61 days with daily intramuscular injections of 20 mg. of progesterone. One patient was given 100 mg. of anhydrohydroxy progesterone by mouth daily for eight weeks.

All four of these patients have come to surgery. There was no decrease in the size of the fibromyomata. Many of the fibromyomata showed microscopic evidence of regression.

Three additional patients have been implanted with 7 or 8 200 mg. pellets of progesterone. They have been followed from one to six months but none have as yet come to surgery.

There has been no significant interference with the menstrual cycles. Urinary gonad stimulating hormone and 17-ketosteroid excretion have also not deviated significantly from the pretreatment values.

3. Distortion of the Spiral Artery in the Ovary in the Presence of Corpus Hemorrhagicum Cysts After Administration of Gonadotropins to Rabbits.

S. R. M. Reynolds, Carnegie Institute of Washington, Department of Embryology, Baltimore 5, Md.

The terminal arterial supply of the ovary arises from the coils of one or two spiral arteries lying along the hilus of the ovary. This arrangement, it has been surmised, lowers arterial blood pressure within the ovary to near-osmotic levels, and equalizes it throughout the ovary. After injection of gonadotropins, the coils become "paid out" evenly during the initial response of ovulation, luteinization, and generalized follicular growth. Accordingly, the spiral arrangement of the main arterial supply to the ovary permits ready adjustment to an increase in length of the ovary.

In a series of rabbits receiving gonadotropins, and sacrificed at twenty-four hour intervals, a certain number showed fresh corpora hemorrhagica. Within the first twenty-four hours, the coils were evenly extended regardless of whether or not fresh small corpora hemorrhagica were present. It was observed that whenever large corpus hemorrhagicum cysts (measuring from about 2 to 3 millimeters across) were present two to six days after injection the cysts were distal to a region of disruption in the orderliness of the coils. Recent cysts have been seen on the ninth day which were associated with symmetrically arranged spiral arteries as well as with ones which were disrupted.

All specimens were injection-corrosion preparations in which vynilite was used as the injection mass. The preparations were studied from stereoscopic photographs enlarged two or three times.

4. Gonadal Stimulation Following the Administration of Antigonadotropic Serum.

Herbert S. Kupperman, Roland K. Meyer and J. C. Finerty. From the Zoological Laboratories, University of Wisconsin, Madison, Wisconsin, and the University of Georgia School of Medicine, Augusta, Georgia.

Antigonadotropic serum obtained from rabbits injected with aqueous (unfractionated) extracts of sheep pituitary was administered to immature rats. The serum was injected for a period of 10 days to two groups of rats, one and ten days old, respectively. Vaginal introitus occurred in the animals treated with antigonadotropic serum 3-4 weeks prior to that in the littermate control. Patency of the vagina occurred, on an average, 10.9 days after cessation of antigonadotropic therapy. Associated with the observed precocious sexual maturity there was marked ovarian and uterine stimulation over and above that seen in the control females. Basophilic changes were observed in the pituitary

glands after the ten day treatment with antihormone. However, gonadotropic assays performed at this time showed the pituitary of the antihormone-treated rats to contain less gonad-stimulating substances than that of littermate controls. These data demonstrate that precocious sexual maturity, endogenous in origin, may be the result of morphological changes induced in the hypophysis of the injected animals. The data present evidence that the ovary of the sexually immature rat secretes a gonadal hormone, the absence of which will cause basophilism in the anterior pituitary.

5. Liver and Gonadal Changes Following the Administration of Carbon Tetrachloride to Male Rats and Female Guinea Pigs.

Boris Krichesky, S. J. Glass, E. Furlong and M. Feiner, Department of Zoology, U.C.L.A.

Previous experimental and clinical observations suggest:

1. That a liver-gonadal syndrome may follow or be associated with sustained and extensive liver damage,
2. That the impairment of gonadal function may be the end result of hepatic failure to inactivate the steroid hormones, especially the estrogens and androgens.

To test this theory, further observations on this liver-gonadal relationship are being reported. It was found that the feeding of carbon tetrachloride to male rats and female guinea pigs was followed by hepatic cirrhosis and gonadal damage in both groups of animals. In the guinea pigs, estrogen excretion is strikingly increased for over 50 days to be followed by a drop within 60 days to pretreatment levels. The ovaries at the terminal phase of this experiment show striking atrophy.

Whether these gonadal effects are a direct result of the liver damage and/or changes in pituitary gonadotropic function is being investigated.

Lantern slides of the various morphologic changes observed in the sequence of progressive liver and sex organ damage will be shown.

6. Clinical Evaluation of Dienestrol, a Synthetic Estrogen.

A. E. Rakoff, K. E. Paschkis and A. Cantarow. Jefferson Medical College and Hospital.

Dienestrol (4:4′ dihydroxy-γ-σ-diphenyl-β:σ-hexadi-) was evaluated in 82 patients with various conditions in which estrogen therapy was indicated with reference to clinical improvement, objective response, and evidences of toxicity.

In 40 menopausal women dienestrol afforded excellent relief in every instance, the minimal dosage necessary ranging from 0.1 to 1.0 mg. with an average of 0.43 mg. daily. However, the average dosage required to improve the deficiency smear to a slight estrogen effect was 0.77 mg. while to produce a marked estrogen effect required much higher dosages. Bleeding during the course of treatment or on withdrawal occurred only twice on therapeutic dosages and in two other cases with higher dosages. It was difficult to induce bleeding in younger women with amenorrhea even with high dosages. In 26 postpartum patients inhibition of lactation was readily obtained with dosages of 1.0 mg. daily for 3 days and 0.5 mg. thereafter for 1 week. These findings suggest that dienestrol has a relatively marked inhibiting effect on the pituitary.

No symptoms of intolerance to dienestrol were noted in any patient even in high dosage. In 25 patients treated for 4 to 12 months (average 6½ months) no evidences of toxicity were noted nor any significant changes in blood count, urinalysis, or liver function studies.

7. Diethylstilbestrol Dipalmitate in Aqueous Suspension.

S. Charles Freed, Department of Medicine, Mt. Zion Hospital, San Francisco, California.

We have demonstrated that there are at least two advantages in preparation of fat soluble crystalline sex hormones suspended in aqueous medium (estrone, stilbestrol and testosterone). These advantages are freedom from the allergic reactions of the usual oil vehicle and increased therapeutic effectiveness through a delay in absorption of the aqueous suspension over that of the oil solutions. Diethylstilbestrol dipalmitate, a slowly absorbed estrogen with prolonged action was suspended in an aqueous medium to determine whether this possessed the advantages over an oil solution. Five mg. of the material containing 1.6 Gm. of the active component was administered every two weeks to menopausal patients according to the plan established for the other preparations. Eighty-six patients received 242 treatments. There appeared to be no appreciable difference in the beneficial effect of these patients with a comparable number of patients receiving an equal amount of the same material dissolved in oil. Either the oil solution is as slowly absorbed as the aqueous suspension or else there is no enhancement of effect by further slowing down the absorption of this preparation. The only advantage therefore of an aqueous suspension of diethylstilbestrol dipalmitate over that in oil is its freedom from local allergic reactions.

8. The Effect of Diethylstilbestrol Upon Alloxan Diabetes as Related to Food Intake in the Rat.

Dwight J. Ingle. The Research Laboratories, The Upjohn Company, Kalamazoo.

Diethylstilbestrol and other estrogens were found to be diabetogenic in the partially depancreatized, force-fed rat (Ingle, D. J., *Endocrinology* **29**: 838, 1941), whereas Janes and Dawson (*Endocrinology* **38**: 10, 1946) failed to observe a diabetogenic effect of diethylstilbestrol in alloxan-diabetic rats which ate *ad libitum*.

The present experiments show that the effect of diethylstilbestrol upon alloxan diabetes is determined by the intake of food. Male rats of the Sprague-Dawley strain (initial weight, 300 grams) were made diabetic by repeated intraperitoneal injections of 25 mg. of alloxan. All of the animals were fed a fluid medium carbohydrate diet.

When diethylstilbestrol was administered to animals in which the food intake was kept constant by forced feeding, there was a striking exacerbation of the diabetes in every case, and the effect disappeared when the administration of the estrogen was stopped.

Those animals which ate *ad libitum* voluntarily consumed more food than was given by feeding, but when the estrogen was administered the food intake dropped sharply and the amount of urinary glucose was decreased significantly.

9. The Factor of Previous Treatment in Experimental Menstruation.

Doris H. Phelps. Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville, Tennessee.

It has been shown previously that the duration of experimentally induced menstruation can be influenced by a number of factors; among these are the intensity of hormonal stimulus, its composition and the duration of its action. This report deals with a hitherto undescribed factor of great importance, namely, the structure of the endometrial vascular bed at the beginning of the cycle.

To obtain information concerning mechanisms involved in the production of menstrual abnormalities, eight ovariectomized monkeys were injected with various combinations of the ovarian hormones. Endometrial vascular phenomena were observed by means of intraocular endometrial transplants and these observations were correlated with observations on uterine bleeding. One hundred seven cycles of uterine bleeding were produced, 1–13 per monkey. Analysis of the results of each experiment in relation to treatment administered in previous experiments in the same animal revealed that 1)

permanent changes in the structure of the endometrial vascular bed may result from stimulation by the ovarian hormones and 2) the architecture of the endometrial vascular bed at the beginning of any given course of treatment with ovarian hormones exerts an important influence upon the uterine bleeding produced by that course of treatment.

10. Experimental Alteration of the Human Ovarian Cycle by Estrogen.

Willis E. Brown, J. T. Brandbury, A. F. Jennings. University of Iowa, Department of Obstetrics and Gynecology, Iowa City, Iowa.

Patients were treated with stilbestrol at different phases of the cycle to determine its effect on menstrual rhythm and endometrial histology. When a single 20 mg. dose of stilbestrol was given orally in the early proliferative phase (4th to 10th day), the length of the interval was increased to an average of 38 days (range 32–48 days in 14 trials). Twelve untreated cycles in these patients averaged 29 days in length (range 24–35 days). Six of the treated cases experienced a very scant vaginal bleeding for a few days starting about a week after receiving the estrogen. The endometrium remained in a proliferative phase until about 10 days before the onset of bleeding and then it exhibited the normal secretory changes. There was one exception, a cycle of 33 days, in which the endometrium did not exhibit any secretory changes, suggesting an anovulatory cycle. Under these conditions, a single large dose early in the cycle seems to delay ovulation about nine days.

Eight patients with dysmenorrhea were treated with oral stilbestrol starting the day after the cessation of menstruation. The dosage was 1 mg. daily for 10 days, 2 mg. daily for the second 10 days, and 3 mg. daily for the third 10 days. With this regimen the patients were relieved of their dysmenorrhea for three successive months and endometrial biopsies indicated that all three cycles had been anovulatory. Two other patients became so nauseated that they discontinued the treatment. One patient experienced a marked increase in weight, due to an edema which subsided quickly after stopping the medication. She then had an interval of 55 days before her next spontaneous menstrual period. Under these conditions, a continuous and increasing dosage for three weeks, it is possible to suppress the luteal phase for as long as three successive months.

When estrogen medication was started in the post-ovulatory phase of the cycle, 5 to 10 mg. of stilbestrol per day, there was no appreciable alteration of the luteal phase or any delay in the onset of menstruation. To date it has not been possible to prolong the life of the corpus luteum by estrogen therapy in the woman.

Papers read by title

11. Studies on the Variations of Blood Gonadotropins and Vaginal Smears During Pregnancy in Correlation with the Fetal Sex.

H. E. Nieburgs, H. S. Kupperman and R. B. Greenblatt, Department of Endocrinology, University of Georgia, School of Medicine, Augusta, Ga.

The investigation of vaginal smears in 253 women during the 8th to 36th week of pregnancy revealed a progressive proliferation of the vaginal epithelium due to increased estrogen activity. This is accompanied by increased glycogen deposition and massive desquamation of cells due to the action of progesterone. In addition to these progressive changes in the vaginal mucosa a number of specific smear types were observed. These were grouped into the mucoid-cornified, glycolytic and plasmolytic smears. There was no correlation of these smears with threatened abortions or toxemias. Where specific smear types were present the sex of the infant was predetermined with an accuracy of 85.4 per cent.

In a further group of pregnant women assays of blood gonadotropins were carried out on 21-24 day old mice, estimating the FSH and LH fraction. The amount of FSH present was mainly constant, somewhat decreasing towards the later stages of pregnancy. (The determinations were made for dilution of serum up to 1:40.) With the method employed the effect of LH was either totally absent or was present in dilutions up to 1:10 and rarely in dilutions of 1:20.

Data is presented on the relation of blood gonadotropin levels to the sex of the fetus.

12. Oral Estrogen Therapy During Menopause.

Abbey David Seley, Deborah Baumgold and Samuel Vernick. Gynecological Endocrine Department, Hospital for Joint Diseases, New York City.

Management of the menopausal state by oral estrogens alone was begun on July 1, 1943 in the Gynecological Endocrine clinic of the Hospital for Joint Diseases. For the past three and one half years not a single injection of any estrogenic substance has been given. Since oral estrogens are derived from various sources and/or have different chemical structures, a comparative clinical study of 90 unselected and consecutive menopause patients was initiated in order to evaluate the effectiveness of these substances. The purpose of this report is to indicate the relative value of the various estrogenic substances used in regard to: (1) ability to control the neurocirculatory disturbance characteristic of the menopause; (2) the rate of change of the vaginal smear; (3) the possibility of carcinogenic alteration when estrogens are used in doses sufficient to control the menopause as evidenced by endometrial biopsy and biopsy or curettage of the cervical stump; (4) the number and type of induced side reactions including bleeding; (5) the final result obtained by the oral route alone a) in the average case and b) in cases complicated by menopausal arthralgia, a number of which are found in this particular hospital.

13. Correlation of Basal Body Temperature Curves with Endometrial Biopsy.

A. R. Abarbanel, Department of Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles, California.

Correlation studies of several hundred endometrial biopsies with the basal body temperature curve for that cycle reveals that on the whole, the classically sharply defined diphasic B.B.T. curve is usually associated with a presumed ovulatory cycle as witnessed by successful conception or a fully developed secretory endometrium.

On the other hand, study of various aberrations revealed a secretory endometrium, especially of the so-called mixed type or immature progestational phase (day 19–22 of a 28 day cycle) when taken of the first day of menses. B.B.T. curves were either irregular or flat.

It is postulated that an immature progestational phase or a mixed type of endometrium does not necessarily represent ovulation but merely various degrees of theca luteinization without concomitant ovulation. In brief, a staircase phenomenon is postulated for the human, similar to that proposed for the macacus rhesus by Hartman.

2:00 P.M. *Viking Room*

14. A Rapid Method for the Determination of Urinary "17-Ketosteroids."

I. J. Drekter, Sidney Pearson and Thomas H. McGavack, New York Medical College, Metropolitan Hospital Research Unit, Welfare Island, New York.

A method for the rapid clinical determination of urinary "17-ketosteroids" in volumes of urine as small as 10 ml. is described. Easily available, inexpensive laboratory equipment is used, and the hydrolysis extraction and assay can be completed within four hours.

Optimum conditions for the hydrolysis and extraction of urine volumes from 10 ml. to 50 are given. Heating at 80° for 10 minutes gives the apparent maximum Zimmerman color producing substances.

The results of extraction with several solvents are given. Ethyl ether gives the best results. Recoveries are good. Normal value of 38 young men between ages of 18–30 by this method range from 10 to 30 with an average of 16.0 mg. excretion in 24 hours.

15. Further Studies on the Metabolism of Therapeutic Doses of the Natural Estrogens in Human Subjects.

Benjamin F. Stimmel and Clair L. Stealy, Rees-Stealy Medical Research Fund, Ltd., San Diego, Calif.

We have shown that our procedure for the chromatographic fractionation and photometric estimation of urinary estrogens can be used to study the metabolism of therapeutic doses (1–2 mg.) of the natural estrogens in human subjects. These studies were made on (a) a normal human female, (b) a bilaterally ovariectomized, hysterectomized human female, and (c) a bilaterally ovariectomized human female. The present report concerns similar estrogen studies on (a) a normal human male and (b) a bilaterally orchiectomized human male. These studies were made to establish a basis for work of a similar nature on human subjects with cancer of the prostate gland. In general, the human male metabolizes therapeutic doses of the natural estrogens in a manner similar to the bilaterally ovariectomized hysterectomized human female. Estriol apparently is not converted to estrone or estradiol, estrone and *a*-estradiol are partially interconvertible and the injection of either leads to the excretion of estriol also, and only a small fraction of the injection material of any of the three estrogens is recovered in estrogenically active forms. The nature and amount of the estrogens excreted are profoundly influenced by (a) the vehicle in which the hormone is administered, (b) the route of administration, and (c) the nature of chemical conjugation of the administered hormone. The presence of the male gonads appears to influence to some degree the manner in which the therapeutic doses of the female hormones are metabolized. From these studies certain conclusions can be drawn regarding the type and amount of estrogenic substances which might prove satisfactory for further studies.

16. A Simple Quantitative Colorimetric Test for Estrogens.

Herman Cohen and Robert W. Bates, E. R. Squibb and Sons, New Brunswick, New Jersey.

The Kober test for estrogens and various modifications thereof, consist of two steps: 1) Initial heating with a small volume of H_2SO_4 mixed with a phenolic compound and 2) dilution with water or aqueous H_2SO_4 and reheating.

Absorption spectrum studies have shown that the presence of phenol, B-napthol sulfonic acid or thiocol does not change the absorption curves from those obtained using H_2SO_4, alone, nor are the extinction coefficients appreciably different. The action of phenol is to quench the green fluorescence which affects the visual appearance of the red color but not the response of the photoelectric cell.

Based on these observations the following simple procedure, omitting the phenol reagent, has been developed.

0.4 cc. of an ethanol solution of estrogen is heated with 2.0 cc. of concentrated H_2SO_4 for three minutes in a boiling water bath. Remove tube from bath and add at once 8 cc. of 25% H_2SO_4 (by volume). Stir and heat the solution again for three minutes at 100°C. Cool in tap water and read the color density in a colorimeter using a 510 mu filter. The

color developed is stable at room temperature for four hours. Beer's law holds between the limits of 5 to 60 gamma of estrone.

The intensities of the color produced with estrone, estradiol and estriol differ, so that quantitative determination of each compound in a mixture requires fractionation.

17. The Application of the Zimmermann and the Kober Reactions Concomitantly to Human Urine

William T. Salter, Department of Pharmacology and Toxicology, Yale University School of Medicine, New Haven, Connecticut.

In order to detect a possible reciprocal interplay between androgenic and estrogenic effects in the organism it is desirable to measure concomitantly various types of steroid hormone. In the absence of suitable methods for their detection in blood, the estimation of urinary steroids offers a possible approach. Because it is impractical to measure the many derivatives known to exist simultaneously in human urines, it becomes necessary to use procedures which record the net effect of large groups of compounds. In addition, microchemical analysis conceivably may be more significant than biological assay because relatively inactive components like etiocholanolone and estriol may represent forms of hormones which originally played important metabolic roles.

As a first approximation the Zimmermann and Kober reactions have been applied together in metabolic studies varying in duration from 6 to 24 hours. Technically, the definitive color in each case is obscured by the presence of extraneous brown pigments. Instead of attempting complete purification of the chromogens, it is convenient to develop the color after partial purification of the extracts. Thereupon, the undesirable pigments may be removed in large measure by differential solubility in appropriate extracts of varied polarity. In the case of 17-ketosteroids it has not been necessary to use an additional optical correction; but with males and non-pregnant females Kober's pigment must be estimated by optical analysis even after preliminary extraction of the final colored compound. Although the Kober pigment fluoresces strongly when in pure solution, a disturbing quenching may be observed in certain contaminated solutions. Therefore thus far the photoelectric colorimeter has been employed for routine work.

It is convenient to locate the concomitant values derived by such procedures on a rectangular graph depicting 17-ketosteroids as abscissae and estrogenic-equivalents as ordinates. When this procedure is followed certain clinical syndromes occupy characteristic positions on the plot.

(This work was aided by grants from the Navy Task Order VI, N6ori-44, The Donner Foundation and the Jane Coffin Childs Memorial Fund.)

18. The Metabolic Pathway of Estriol Production in the Organism.

Max N. Huffman and Arthur Grollman, from the Southwestern Medical College, Dallas, Texas.

The existence of a reversible equilibrium between estrone and *a*-estradiol and the conversion of the former to the latter in the human is well established. The pathway of the conversion of estrone to estriol is still, however, a matter of speculation. It is generally assumed that estrone is enolized and then hydrated to give estriol or that this hypothetical enol compound is formed directly by dehydrogenation of *a*-estradiol. A knowledge of the exact course of estrogen metabolism is important for it may lead to the production of more active naturally occurring estrogens as well as to better concepts of the possible role of these compounds in carcinogenesis and in the body economy in general.

An alternative hypothesis to account for the transformation of estrone to estriol is suggested; viz., that estrone is first converted to 6-keto-estrone which in turn is reduced first to 16-keto-*a*-estradiol and finally to estriol. One of us (M.N.H.) has prepared an epimer of estriol in which both C_{16} and C_{17} have *a*-configurations. This compound has been designated as iso-estriol-A. Reduction of 16-keto-estrone yields four possible stereoisomers, of which three have been prepared. We have determined the estrogenic activities of these compounds as well as of 16-keto-estrone prepared by partial synthesis from estrone. The results permit certain deductions regarding the probable pathway of estriol production in the organism.

19. Color Reactions of the Steroids.

Herbert Jaffe, Babette Solomon, and Robert H. Williams. Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

A systematic survey of various color reactions of the steroids is being made with the principal objective of establishing and evaluating the structional characteristics essential for chromogenicity. Preliminary observations on thirty-seven steroids, comprising bile acids, sterols, androgens, estrogens and corticosteroids, and grouped according to progressive modifications in the nuclear ring substituents and structures, reveal that the following reactions can be associated with specific elements of the steroid structure:

Meta-Dinitrobenzene and Antimony-Trichloride Reactions. The m-dinitrobenzene reagent is specific for ketonic groups present either in the ring or in the side-chair. On the other hand, the presence of hydroxyl groups is essential for chromogenicity with the antimony-trichloride reagent, but the position of the alcoholic groups modifies the hue, intensity and rate of color development. Thus, for example, the hydroxycholanic acid yeilds a positive antimony reaction and a negative m-dinitrobenzene reaction, but the ketocholanic acids react conversely. Ketols varv in their reactivity towards each reagent, depending on the preponderant characteristics and the positions of the substituent hydroxyl and ketonic groups.

It is to be noted further that other polyvalent metals, viz. iron and aluminum (somewhat soluble in organic solvents as their chlorides) may replace antimony, effecting similar color changes.

20. Chemical Assay of Urine for Adrenocortical Hormones in Endocrine and Non-endocrine Diseases.

William H. Daughaday, Herbert Jaffe and Robert H. Williams.

In determining the quantity of adrenocortical hormones in urine, we have adopted the principle proposed by Lowenstein of measuring the formaldehyde liberated by the oxidation of urinary extracts with periodic acid. However, with Lowenstein's procedure certain substances in the urinary extracts interfere with the color reaction with chromotropic acid. To circumvent this difficulty, it is possible to distill the formaldehyde into a sulfite solution. A pure purple color is then obtained by the reaction with chromotropic acid and this is measured in an Evelyn photocolorimeter. We have used this method in 75 determinations. The results have been expressed as milligrams of adrenocortical hormone per 24 hours. Excretion by healthy adults has averaged 1.2 mg./24 hours (range 1–1.5 mg./24 hours). Four patients with Addison's disease averaged 0.5 mg./25 hours. Two cases of Cushing's syndrome were 2.8 and 23 mg./24 hours. In 9 patients with exogenous obesity the excretion was normal, but in two determinations it was above normal. Low values were found in either hyper- or hypothyroidism. Hypopituitarism was as-

sociated with levels intermediate beween Addison's disease and normal. Decreased excretion was also found in one patient with Waterhouse-Friderichsen syndrome and in one patient with scurvy.

21. Disappearance of Diabetes Mellitus Associated with Acromegaly Following Acute Mastoiditis and Basilar Meningitis.

T. P. Almy and Ephraim Shorr. Russell Sage Institute of Pathology, the Department of Medicine, Cornell University Medical College, and The New York Hospital, New York City.

Complete disappearance of diabetes mellitus was observed in a 40-year old male with acromegaly of 14 years duration, the last 5 being complicated by diabetes and impotence. A 4+ glycosuria was regularly present despite 60 units protamine insulin daily. An oral glucose tolerance test gave the following blood sugar values: fasting, 250; 1 hour, 455; 2 hours, 555 and, 3 hours, 500 mg. %.

He then developed acute right mastoiditis and petrositis, basilar meningitis, retinal hemorrhages, visual field defects and ophthalmoplegia. On the 18th day of the illness, for which mastoidectomy was performed, the urine became sugar-free and fasting blood sugar and sugar tolerance curves had returned to normal levels. He has now remained free of diabetes for 5 years.

The BMR has fallen to −30% with no alteration, however, in serum cholesterol. There is no evidence of adrenal insufficiency. Impotence, associated with urinary 17-ketosteroid values of 2.5 mg., has persisted, except during androgenic therapy. Three years after this episode, the sella was found reduced in size.

The sudden disappearance of diabetes is attributed to partial degeneration of the anterior pituitary, during the acute infectious episode, with a consequent reduction in the elaboration of the diabetogenic principle.

22. True Hermaphroditism: Report of a Case with An Ovotestis, and Endocrine Studies.

John C. Weed (by invitation), A. Segaloff, Wm. Wiener (by invitation) and J. W. Douglas (by invitation). From the Divisions of Gynecology and Medicine, The Charity Hospital of Louisiana at New Orleans and the Alton Ochsner Medical Foundation, New Orleans, Louisiana.

A colored "female," age 36, exhibiting feminine bodily contours and feminine social adjustments, was found to have an enlarged clitoris, masculine facial hair distribution, and abnormal external genitalia. In a large hernial sac, an ovotestis was found associated with an atrophic uterus, left tube and ovary. Biopsy sections of the latter revealed normal ovarian stroma and a small Brenner tumor. Sections of the ovotestis which was completely removed, revealed normal ovarian stroma, definite testicular tubules without spermatogenesis, and large islands of interstitial cells. A rudimentary epididymis and fallopian tube were found in the hernial sac. Preoperative determinations of the gonadotropic hormone and of 17-ketosteroids were made on 24 hour urine collections, and these were repeated postoperatively. The gonadotropic hormones remained essentially unchanged in both series of assays. The 17-ketosteroid determinations were 7.5 and 7.6 mg. per 24 hours preoperatively and from 4.8 to 5.6 mg. per 24 hours postoperatively.

23. Testosterone in a Case of Polyostotic Fibrous Dysplasia.

Rita S. Finkler and George M. Cohn. From the Endocrine Clinic and Service, Newark Beth Israel Hospital, Newark, New Jersey.

A case of polyostotic fibrous dysplasia observed over a period of several years is reported. The patient was referred for treatment to the Endocrine Service at the age of 13

after 4 years observation in other clinics. The most disturbing symptoms were progressive loss of vision in the right eye due to pressure of fibrous hyperplasia of the maxillary area upon the contents of the right orbit and progressive facial asymmetry. Since the disease is said to be self limiting at maturity, it was decided to attempt hastening maturity by the administration of testosterone propionate, because of the progressively failing vision. After one year of therapy, beginning June 1941, periodic examinations revealed gradual improvement in vision due to regression of bone pathology of the right orbit and a regression of the fibrous dysplasia in other bones of the body. At the last examination, in September 1946, there was almost complete recovery of vision in the right eye and regression of bone pathology in other parts of the body. It is felt that the use of testosterone propionate hastened maturity and the period of recession in this case since prior to treatment it was estimated that regression would not commence until after the age of 15.

24. Bilateral Arrhenoblastoma Without Masculinization, Adenoma Testiculare of Pick.

Minnie B. Goldberg and Alice F. Maxwell, San Francisco.

Case Report

This report deals with a 19 year old girl presenting a paradoxical picture of primary amenorrhea, tall eunuchoid build, *large breasts*, poorly developed external genitalia with rudimentary vagina, congenital absence of uterus and cervix, absent axillary and scant pubic hair and a high urinary gonadotropin titer. The adnexa were not palpable.

Prior to performing a vaginal plastic operation surgical exploration of the pelvis was carried out with the surprising finding of bilateral, poorly developed gonadal structures composed of tissue grossly resembling adrenal cortex. This, on microscopic section, proved to be a highly differentiated type of arrhenoblastoma. Careful search revealed no evidence of ovarian tissue. Both tumors were removed. Bilateral rudimentary structures suggesting the unfused anlage of uterus were also demonstrated.

The source of the estrogens responsible for the breast development remains a mystery. This case brings up many interesting questions concerning sex determination and differentiation involving problems in genetics, endocrinology and intersexuality.

Illustrated with photographs, photomicrographs and slides.

Papers read by title

25. Social and Psychological Readjustment of a Pseudohermaphrodite Under Endocrine Therapy.

Rita S. Finkler, Newark, New Jersey.

An intersex individual, aged 21, raised as a female, failed to develop either male or female secondary sex characteristics at puberty. The patient was asthenic and lacked endurance and energy, but excelled scholastically. The psychological status was of masculine pattern. He was fairly content until the age of 19, when he developed an emotional attachment for a girl and at the same time became aware of an enlarged clitoris. This discovery was somewhat of a shock and produced emotional conflicts resulting in symptoms of anxiety neurosis which lasted for over 2 years until a thorough investigation revealed the individual to be an "unfinished male." The investigations consisted of bio-assays, psychological analyses and exploratory laparotomy. Intensive substitution therapy with various testosterone compounds developed male secondary sex characteristics, and brought about a marked improvement in the patient's general health, energy, endurance and outlook on life. The patient was stimulated to still further scholastic and

intellectual achievement. As long as therapy was continued, the patient's physical and psychological status continued to improve. Interruption in therapy for any appreciable length of time resulted in diminution of energy, endurance and mental alertness. Lantern slides.

26. Some Observations on the Utilization of a Liquid Chromatogram Technique in the Colorimetric Estimation of Urinary Pregnanediol.

Benjamin F. Stimmel. From the Rees-Stealy Medical Research Fund, Ltd., San Diego, California.

In our preparation of urinary phenolic residues for chromatographic fractionation of the estrogens, a neutral fraction of the ether soluble material is obtained. This fraction may be utilized for colorimetric (H_2SO_4) pregnanediol determinations in a procedure in which the chromatogram technique has been incorporated. Aqueous solutions of pure pregnanediol glucuronidate similarly treated have been found to yield two separate chromatographic fractions which respond to the color reagent. One of these is so weakly bound to the column of activated alumina that it appears in the initial benzene filtrate whereas the second (pregnanediol) requires much stronger eluting agents (2% methanol-benzene). It is hypothecated that a portion of the pregnanediol loses one or more of its hydroxyl groups during hydrolysis of the glucuronidate as has been shown to occur with alcoholic 17-ketosteroids under similar conditions. This partial destruction of the pregnanediol molecule is maximal during hydrolysis by autoclaving and minimal during simultaneous extraction and hydrolysis as described by Astwood et al. The use of the latter hydrolysis technique on our aqueous extracts of the butanol residues permits satisfactory colorimetric estimation of the pregnanediol content of both pregnancy and nonpregnancy urine. It appears that the method is sufficiently sensitive to detect pregnanediol excretion in a bilaterally ovariectomized human female following the injection of 10 mg. of progesterone. Some studies on pregnanediol and estrogen excretion by patients under simultaneous treatment with therapeutic doses of natural estrogens and progesterone will be presented.

27. The Oral Use of Crude Adrenal Cortex in the Stimulation of Growth of the Face, Particularly the Condyle of the Mandible.

Francis M. Pottenger, Jr., Monrovia, California.

This paper consists of a compilation of the results of a study of a group of patients who have been on adrenal cortical material for periods of two years or more. It encompasses some of our work over a fifteen year period.

Briefly stated, in patients taking the crude adrenal cortex regularly, we have noticed a definite increase in the development of the middle third of the face, but particularly in the length and thickness of the ramus of the mandible, and secondarily in the forward movement of the body of the mandible.

SATURDAY, JUNE 7

9:00 A.M. *Viking Room*

28. Chemical and Cytochemical Studies of the Rat's Adrenal Cortex Following the Administration of Pituitary Adrenocorticotropic Hormone (ACTH)

Helen Wendler Deane (by invitation) and Grace E. Bergner (by invitation). (Introduced by E. W. Dempsey.) Department of Anatomy and Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston, Massachusetts.

Purified pituitary adrenocorticotropic hormone (Armour), containing minimal oxy-

tocic activity, was injected into fasting adult male rats at varying doses and for varying periods of time up to twenty-four hours. Hypertrophy of the adrenal glands and atrophy of the thymus were observed with 2½ mg. of ACTH given every six hours for four doses. Adrenal cholesterol was decreased, and liver glycogen was increased.

Adrenals were fixed in formalin, and frozen sections were stained with sudan IV and Schiff's reagent, and unstained sections were studied for fluorescence and birefringence. Positive reactions by these methods characterize ketosteroids (Cf. Dempsey and Wislocki, *Physiol. Rev.* **26**: 1, 1946). In ACTH treated animals, birefringence and sudanophilia declined noticeably in the zona fasciculata of the adrenal cortex; whereas fluorescence and the Schiff reaction remained normally intense. Shorter treatment with 10 mg. ACTH or smaller doses of ACTH resulted in similar but less marked changes. These observations indicate that the zona fasciculata of the adrenal cortex is under pituitary control and secretes steroid hormones which influence thymus size and glycogen deposition in the liver.

29. Changes in Circulating Leukocytes Induced by Pituitary Adrenocorticotropic Hormone (ACTH) in Man.

A. Gorman Hills (by invitation), Peter H. Forsham (by invitation), and Clement A. Finch (by invitation.) Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston.

The effect of purified adrenocorticotropin (Armour) upon blood elements was studied in normal subjects and in patients with Addison's disease. Intramuscular injections of 25 mg. of ACTH at 8:00 a.m. was preceded and followed four hours later by blood counts including direct eosinophil enumeration. Absolute polymorphonuclear, lymphocyte, and eosinophil counts four hours after ACTH were expressed as per cent of initial values.

In eight normal subjects ACTH administration induced an increase in neutrophils (90 per cent), a decrease in lymphocytes (40 per cent), and a decrease in eosinophils (78 per cent); whereas similar treatment in eight patients with Addison's disease was accompanied by only a slight increase in neutrophils (15 per cent) without a significant change in lymphocytes or eosinophils. Administration of 20 mg. of Compound F (17-hydroxycorticosterone) intramuscularly in four of these patients was followed by increased neutrophils (129 per cent), decreased lymphocytes (53 per cent), and decreased eosinophils (76 per cent). With Compound A (11-dehydrocorticosterone), 50 mg., these changes were mimimal. No effect was observed with 11-desoxycorticosterone (10 to 20 mg.).

It follows that an increase in adrenal cortical hormone level is accompanied by significant hematological changes, viz. an increase in circulating neutrophils and a decrease in lymphocytes and eosinophils.

30. Results of Administration of Anterior Pituitary Adrenocorticotropic Hormone to a Human Subject.

Harold L. Mason, Marschelle H. Power, Edward H. Rynearson, Letizia C. Ciaramelli, Choh Hao Li and Herbert M. Evans. Mayo Foundation, Rochester, Minnesota, and Institute of Experimental Biology, University of California, Berkeley, California.

A young woman was maintained on a constant diet while receiving intramuscularly 25 mg. of adrenocorticotropic hormone daily for six days, 50 mg. for six days and 100 mg for 11.5 days, given in five divided doses each day. Excretion of sodium, potassium, chloride, phosphorus, total nitrogen, creatine, creatinine, 17-ketosteroids and cortin-like

substances was measured daily and that of pregnanediol, estrogen and gonadotropic hormone at intervals. Levels of sodium, potassium, chloride, CO_2-combining power, cholesterol, ascorbic acid, protein, hemoglobin and alkaline phosphatase, the hematocrit and erythrocyte and lymphocyte counts were determined at intervals. During the first two periods the only significant change was an increase in the excretion of cortin-like substances from an average control value of 0.180 mg. to average values of 0.255 and 0.387 mg., respectively. When 100 mg. per day was given the excretion of cortin-like substances increased to 1.44 mg. on the tenth day and the excretion of 17-ketosteroids increased from an average control value of 4.85 mg. to 15.5 mg. on the tenth and eleventh days. There was also a slightly increased nitrogen excretion, a decreased creatine excretion and a pronounced fall in hemoglobin. Other changes were miminal and of equivocal significance.

31. Metabolic Changes Following the Administration of Pituitary Adrenocorticotropic Hormone (ACTH) in Man.

George W. Thorn, F. T. Garnet Prunty (by invitation), and Peter H. Forsham (by invitation). Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston.

Purified adrenocorticotropin (Armour), 2 gamma giving a positive test by the method of Sayers and Sayers, with oxytocic activity of 0.12 units per mg., was administered to a male aged forty-six with partial reduction in pituitary function. On a constant dietary regimen, the patient was given 10 mg. of ACTH in saline (pH 9) every six hours intramuscularly for six days (40 mg. daily). Peripheral vasoconstriction, bradycardia, and abdominal cramps occurred following each injection.

The following changes were observed:

Increased 11-oxy-steroid excretion (sevenfold)
Increased 17-ketosteroid excretion (fivefold)
Increased uric acid excretion (102 per cent)
Increased total nitrogen excretion (45 per cent)
Transitory increase in potassium and phosphorus excretion
Decreased sodium excretion (68 per cent)
No change in creatinine excretion
Increased fasting blood sugar level
Elevated glucose tolerance curve
Decreased serum inorganic phosphorus
Increased serum sodium and carbon dioxide combining power
Decreased plasma protein concentration
Decreased serum uric acid level
Increased polymorphonuclear leukocytes
Decreased lymphocytes and eosinophils

Control studies with pituitrin failed to show any of the above changes with the exception of hemadilution.

32. Urinary Uric Acid-Creatinine Ratio Following Administration of Pituitary Adrenocorticotropic Hormone (ACTH) as a Simple Test for Adrenal Cortical Function.

Peter H. Forsham (by invitation), F. T. Garnet Prunty (by invitation), and George W. Thorn. Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital, Boston.

Earlier studies indicated that an increase in uric acid excretion with a rise in uric

acid-creatinine ratio constituted one of the most consistent findings which followed the administration of the 11-oxy adrenal steroids (Compounds A and F) in man. The same changes have been found to accompany the administration of adrenocorticotropin (Armour) in ten normal subjects, in five patients with miscellaneous diseases without evidence of adrenal insufficiency, and in two patients with anterior pituitary deficiency.

In contrast, it was noted that the maximum increase in uric acid-creatinine ratio following ACTH therapy in eight patients with Addison's disease did not exceed the minimum increase observed in the control group; whereas the administration of either Compound F (20 mg.) or Compound A (50 mg.) induced a significant increase in the uric acid-creatinine ratio in these patients. The presence of renal impairment limits this test for adrenal cortical *reserve* function.

33. Further Studies on the Protective Power of Adrenal Preparations Against Bacterial Toxins.

Lena A. Lewis and Irvine H. Page. From the Research Division of the Cleveland Clinic Foundation, Cleveland, Ohio.

Determination of the relative protective power of adrenal extracts and steroids against typhoid vaccine in adrenalectomized rats has been shown to be a satisfactory method of estimating toxic protection power of hormones.

It seemed desirable to determine whether these substances would be effective in protecting adrenalectomized rats against other types of toxin and to compare the minimal lethal dose (M.L.D.) of the toxin as determined on normal and adrenalectomized rats as a possible means of evaluating the relative importance of adrenal activity in different infectious processes.

Streptococcus toxin, diphtheria toxin, crystalline tetanus toxin, and typhoid vaccine were tested. The streptococcus toxin was non-lethal to either normal or adrenalectomized rats in doses as large as 2.5 ml. of concentrated toxin. The M.L.D. of diphtheria toxin was 5 times as great for normal as adrenalectomized rats, while that of typhoid vaccine was 25 times as great for the normal. No difference could be demonstrated between the M.L.D. of crystalline tetanus toxin for normal and adrenalectomized rats, 60 units killing 100 per cent in both groups.

In adrenalectomized rats, larger doses of adrenal extract or 11-dehydrocorticosterone acetate were required to protect against 1.33 M.L.D. of diphtheria toxin than against 1.33 M.L.D. typhoid. No protective power of adrenal extract against tetanus toxin could be demonstrated. Studies to determine possible protective power of adrenal extract against bacterial peritonitis in mice are being carried out.

34. Effect of Testosterone Upon the Excretion of Glycogenic Corticoids.

E. H. Venning and J. S. L. Browne. From the McGill University Clinic of the Royal Victoria Hospital, Montreal.

The excretion of urinary glycogenic corticoids was followed in a series of 8 individuals before and after the administration of testosterone propionate or of methyl testosterone. Of these cases two were normal individuals, two were patients with Cushing's Syndrome, and the others suffered from hirsutism, diabetes, and one was a patient with lupus erythematosus disseminatus.

The administration of testosterone caused a lowering in the excretion of glycogenic corticoids in all cases with the exception of one of the patients with Cushing's Syndrome. In no case were the glycogenic corticoids depressed below the limit of normal values.

35. Hepato-Renal Factors in Circulatory Homeostasis: XVIII Relation of Adrenals to Formation of a Renal Vaso-excitor Principle.

B. W. Zweifach, Ephraim Shorr, Silvio Baez and S. Rosenfeld. From the Depart-

ment of Medicine, Cornell University Medical College and The New York Hospital, New York City.

An inter-relationship has been demonstrated between the adrenals and the renal mechanism which elaborates the vaso-excitor principle (VEM) which we have detected in blood during the compensatory phase of shock and the acute phase of renal hypertension.

VEM is produced by kidneys from normal animals under reduced oxygen tensions *in vivo* and *in vitro*, and by kidneys of hypertensive dogs, both anaerobically and aerobically. It is detected by its potentiating effect on the response of the terminal mesentery blood vessels to epinephrine.

Following bilateral adrenalectomy (rats, rabbits, dogs) the renal capacity to form VEM became progressively impaired. Three procedures were employed: (1) adrenalectomy; (2) adrenalectomy plus high NaCl intake; (3) adrenalectomy plus NaCl and DCA (0.1 mg./kg. daily).

The mesenteric blood vessels of adrenalectomized rats exhibited a progressive unresponsiveness to epinephrine as adrenal insufficiency developed. *In vitro* incubation of kidney slices from adrenalectomized animals revealed progressive impairment of VEM formation even in animals maintained on high salt intakes. Kidneys removed from adrenalectomized animals maintained on NaCl and DCA for 10–15 days postoperatively behaved like normal kidneys in respect to VEM formation.

36. The Role of the Adrenal Cortex in Protein Catabolism Following Trauma.

C. G. Toby and R. L. Noble (introduced by J. B. Collip). Research Institute of Endocrinology, McGill University, Montreal, Canada.

Trauma (limb clamping) in the rat caused a marked excretion of urinary nitrogen. This was not increased by repeated cortin administration.

Nitrogen excretion in the normal rat was only moderately increased after treatment with a total dose of cortical extract equal to 240 dog units administered over 8 hours.

Nitrogen excretion in the adrenalectomized rat varied depending on the time after operation. It was slightly elevated by 4 days, and had returned to normal after two weeks.

Trauma when applied to the adrenalectomized rat did not cause any increased loss of urinary nitrogen.

Suitable treatment of traumatized rats with cortical extract allowed a practically normal response in nitrogen excretion to occur. The same treatment did not cause increased nitrogen loss in untraumatized adrenalectomized rats. Desoxycorticosterone acetate or hypertonic saline therapy were ineffective.

The experimental results indicate that following trauma, secretion of cortin is not responsible for the increased loss of nitrogen. On the other hand, nitrogen loss does not occur in the absence of the adrenal glands unless replacement therapy with cortin is administered. Adrenal cortical secretion is apparently necessary for the mechanism concerned to operate normally although such secretion per se is not responsible for the increased protein catabolism.

37. A New Hormone of the Adrenal Cortex.

Frank A. Hartman, Katharine A. Brownell and Jonathan S. Thatcher. Department of Physiology, The Ohio State University, Columbus.

The movement of fat from the reserves of the liver during inanition depends upon the adrenal cortex since it fails to occur if the latter is destroyed. The substance responsible, which we propose to call the "fat factor," has been separated from the sodium and carbohydrate factors by chromatographic adsorption. It causes deposition of fat in the

liver of an adrenalectomized animal during starvation, while the other factors do not. Likewise, the crystalline compounds, corticosterone, 11-dehydrocorticosterone and 11-dehydro-17-hydroxycorticosterone, are unable to do this. Further evidence that the carbohydrate and fat factors are distinct has b ... obtained from animals whose adrenals have been enucleated. The output of these factors reaches a point above normal one or more weeks after enucleation. However, the maximum increase for the fat and carbohydrate factors develops at widely different times.

38. STUDIES ON OBESITY.

Robert H. Williams, William H. Daughaday, Walter F. Rogers, Jr., Samuel P. Asper, Jr., and Beverly Towery. Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

Since obesity is often of major consequence and is not, on the whole, satisfactorily controlled, we have used recently available methods in the reinvestigation of certain phases of this aged problem.

The protein-bound iodine of the plasma, determined in 24 patients with marked obesity but with basal metabolic rates above −7 per cent, was found to be normal in 33 per cent, but in 67 per cent it might be considered subnormal, varying from 1.3 to 4.4 gamma per 100 cc. of plasma, with an average of 3.3 gamma. None of the patients had clear-cut clinical evidence of hypothyroidism and none had a goiter.

The excretion of ketosteroids in the urine was subnormal in 9 of 13 patients tested. The "corticosterone" excretion was found to be essentially normal. The glucose-insulin tolerance test yielded evidence of resistance to insulin in each of 8 patients.

Several weeks after removing each of the endocrine glands of rats, estimations of the "neutral fat" of the carcass showed no appreciable increase in the fat content. Moreover, no striking fat deposition resulted from the administration of large doses of the hormones in common use.

Over 100 markedly obese individuals were treated with from 1 to 7 compounds, including 2-amino-6-methylheptane, dextroamphetamine, 1-cyclohexyl-2-aminopropane, p-hydroxy-alpha-methylphenethylamine hydrobromide, laevo-amphetamine, and d-desoxyephedrine hydrochloride. Of these compounds, the first two were the most satisfactory. The anti-obesity effect was apparently due to the decreased hunger and the increased exercise which the drugs produced.

Papers read by title

39. PELLET THERAPY WITH DESOXYCORTICOSTERONE ACETATE IN ADRENAL CORTICAL INSUFFICIENCY.

George F. Koepf and (by invitation) Raymond Kibler. Departments of Medicine and Physiology, University of Buffalo, School of Medicine.

During the five year period (1941–1946) thirty-two patients with adrenal cortical insufficiency were treated with subcutaneously implanted pellets of desoxycorticosterone acetate (Ciba). Although sodium chloride in addition to the normal dietary intake was given during an assay period in which the daily dose of D.O.C.A. in oil was being ascertained, supplementary sodium chloride was seldom found necessary after implantation. Several patients were given adrenal cortical extracts during episodes of acute infections, but in only two cases was it necessary to supplement the therapy for prolonged periods because of severe, repeated attacks of hypoglycemia.

Data to aid in determining the number of pellets was obtained and may be summarized as follows:

(1) The average daily hormone absorption from a 125 mg. pellet (Ciba) by a human is 0.35 mg.
(2) Approximately 60% of the daily dose of D.O.C.A. in oil is required if the D.O.C.A. is given in pellet form.
(3) To determine the number of pellets of D.O.C.A. to implant the following formula is useful:

$$\text{pellets needed} = \frac{\text{daily dose D.O.C.A. in oil} \times 0.60}{0.35}$$

(4) The average duration of each implant was 334 days.

Eighteen of the thirty-two patients were diagnosed as non-specific adrenal cortical insufficiency, and two (11%) of these had died. All of the nine patients with tuberculosis of the adrenal cortex have died, however, some prolongation of life in most of these cases was noted. One (20%) of the five patients with adrenal cortical insufficiency secondary to panhypopituitarism has died.

40. Relationship of Sex Steroids to the Adrenal Glands of Hamsters and Rats. Herbert S. Kupperman and Robert B. Greenblatt.

Sex dimorphism in the size of the adrenal has been reported in the rodents with the female animal exhibiting the heavier adrenal. However, data in the golden hamster revealed a reversal of this sex dimorphism whereby the adrenal of the male hamster was larger than that of the female. Autopsy performed on animals 15 to 600 days of age showed that the adrenal weights were comparable in both sexes until the 30th day of life at which time a sex difference became evident. The adrenal weight in both the male and female animals plateaued at 100 days of age with the weight of the male adrenals recorded at 65% greater than those of the female. The increase in size of the male adrenal coincided with the beginning of androgenic activity as evidenced by the appearance of dimorphic pigmentation in the male and the period of rapid growth of the prostate and seminal vesicles. Administration of sex hormones to castrate and normal male and female hamsters failed to demonstrate a specific action of the sex steroids. The effects of estrogen and progesterone upon the adrenal glands of albino rats were noted after estrogen administration. With the doses employed no hypertrophy of the adrenals was noted after estrogen administration. There was a variation in response to progesterone. The results, together with the morphological findings, are described and discussed in the light of the adrenal-gonad-pituitary relationship.

41. Correlations of Biochemical and Histological Changes in the Adrenal Cortex in Various Types of Disease.

Walter F. Rogers, Jr., and Robert H. Williams. Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

Certain biochemical and physiological changes in the adrenal glands of 103 (selected) patients dying of a wide variety of diseases were compared with the glands of normal individuals who experienced instantaneous or sudden death. The cholesterol content of the adrenal glands was compared with observations made of the tissue with polarized and ultraviolet light. Comparisons were also made of tissues stained with phenylhydrazine, Sudan IV, and phloxine-methylene blue. It is concluded that a close correlation exists in each of these methods of study and while they give an indication of the total amount and distribution of the lipoid deposition in the adrenal cortex, they do not demonstrate the amounts of adrenal hormones present, but they can be used to indicate the functional reactivity of the adrenal cortices in various types of disease.

2:00 P.M. *Viking Room*

42. THE USE OF HYPERTONIC SALINE INFUSIONS IN THE DIFFERENTIAL DIAGNOSIS OF DIABETES INSIPIDUS AND PSYCHOGENIC POLYDIPSIA.

Anne C. Carter and Jacob Robbins (introduced by Ephraim Shorr). From the Department of Medicine, Cornell University Medical College and The New York Hospital, New York City.

Hickey and Hare (*J. Clin. Investigation 23:* 768, 1944) have shown in animals and in a small series of normal human subjects that, after adequate hydration, infusion of 2.5% NaCl (0.25 cc./kg./min. in man) result in reduction in urine flow attributable to an antidiuretic factor of neurohypophyseal origin. This effect was absent in experimental and in two cases of human diabetes insipidus.

Additional evidence of the value of this procedure for differentiating diabetes insipidus from psychogenic polydipsia is provided by studies on a larger series of human subjects, using urine flow as the index. Nine normal hydrated subjects showed a marked reduction in urine flow during infusion of 2.5% NaCl. This reduction was found not to be due to spontaneous decrease in water diuresis nor to saline per se, and could be prevented by overhydration.

Of ten patients with polyuria, two showed reduction in urine flow during infusion and their subsequent spontaneous decrease in urine volume established the psychogenic basis for the polydipsia. The remainder exhibited sustained diuresis during the infusion and a prompt reduction in urine flow following 0.1U Pitressin intravenously indicating true diabetes insipidus. In the absence of renal disease, this test provides for differentiation between psychogenic polydipsia and diabetes insipidus.

43. EFFECT OF AQUEOUS TESTICULAR EXTRACTS ON GROWTH AND DEVELOPMENT OF SPONTANEOUS MAMMARY TUMORS IN THE AGING BITCH.

F. X. Gassner. Colorado Agricultural Experimental Station, Fort Collins, Colorado.

An aqueous testicular extract of fresh beef testes, devoid of lipoids and essentially so of protein, was assayed for androgenic properties in intact and castrated male rats, and for estrogenic potency in castrated female rats. Each cc. of the extract represented 10 Gm. of fresh testes.

The sex organs of castrates of both sexes failed to show any response. The seminal vesicles, prostates and testes of the intact males were reduced in weight up to 46 per cent.

Nine aging female dogs with spontaneous mammary tumors received intramuscularly 10 cc. aqueous testicular extract weekly for up to eight weeks. Biopsies were taken at the start and at the end of treatment. Changes in the size of the tumors were photographically recorded weekly. In seven dogs the rapid growth of the tumors was not only arrested but their size was reduced as much as 86 per cent. The initial biopsies showed the presence of adenocarcinomas grades 1 to 3. After 6 weeks treatment extensive hyalinization of the stroma and necrosis and reduction of the tumorous parenchyma were evident. Decided improvement in behavior and well-being of the dogs was noted.

Gynecomastia in one intact male dog and in one castrated male cat subsided after 4 weeks treatment. The probable mechanism involved is discussed.

44. CONJUNCTIVAL AND CORNEAL LESIONS IN HYPERCALCEMIA.

John Eager Howard and Frank B. Walsh. From the Departments of Medicine and Ophthalmology, the Johns Hopkins University and Hospital, Baltimore, Maryland.

In the past few years we have seen, in approximately 50 per cent of our patients with

hypercalcemia, distinctive phenomena in the eyes which are believed to be of diagnostic importance and theoretical interest. Similar lesions have been observed by colleagues at the Massachusetts General Hospital. The crystals cannot be identified with the naked eye so that examination with the slit lamp is necessary. In the deep conjunctiva of the palpebral fissure area are small glass-like particles. There is likely to be some redness, but this may not be pronounced; and there may or may not be complaint of conjunctival irritation. The crystals may be numerous or few. In one instance here and in several instances at the Massachusetts General Hospital, the superficial layers of the cornea have been involved presenting an appearance resembling band-shaped keratitis. Biopsy of one case was studied at the Johns Hopkins University and the crystals reported to be calcium phosphate. The crystals are clear and not at all like the grayish patches sometimes seen extending superficially over a pterygium. The lesions have been seen by us in instances of hyperparathyroidism and vitamin poisoning. In some instances the deposits have disappeared after the metabolic disturbance had been corrected.

Why the conjunctival and corneal membranes should be so involved is not clear. The factor common to our cases seems to be hypercalcemia, the serum phosphorus levels having been normal, high and low. Search for such lesions by ophthalmologists may uncover cases with hypercalcemia which would otherwise have been overlooked by the internist.

45. A Secondary Sexual Character That Develops in an Organ Common to Both Sexes But Normally Only in Men. With a Discussion of the Relation of This Character to Endocrine Stimulation.

James B. Hamilton, Long Island College of Medicine, Brooklyn, New York.

In organs present in both sexes only relative differences in secondary sex characters have been described. That is, a character is developed to a greater extent or occurs more commonly in one sex. Some interest attaches, therefore, to a masculine trait which distinguishes *absolutely* between normal men and women. This character is the growth of terminal (coarse) hairs on the external ear.

Three factors control development of this trait: aging, endocrine stimulation (apparently androgenic) and genetic predisposition. Large auricular hairs grow in Caucasian men after the 24th year and increase in frequency and coarseness until by the 55th year 75 per cent of men exhibit this character (229 men studied). Terminal hairs were not observed in a series of 105 women and 50 eunuchs. Auricular hairs appeared in three of five eunuchs receiving androgenic treatment and in three of five women with pronounced virilism.

Pronounced hairiness depends more upon age and inheritance than any exceptional degree of androgenic stimulation. No terminal auricular hairs were observed in undoubtedly virile men among 54 American Indians, 84 Chinese and certain Caucasian families. Titers of urinary steroids in 57 normal Caucasian men bore no quantitative relationship to the amount of auricular hair.

46. The Use of Methyl Testosterone and Testosterone Propionate in Premature Infants.

E. Kost Shelton and Jerome S. Mark. From the University of Southern California and the Shelton Clinic, Los Angeles, California.

Following a preliminary report by E. Kost Shelton, M.D., and Arthur E. Varden, M.D., before the Association for the Study of Internal Secretions, Saturday, June 29,

1946, the experimental use of testosterone, in various forms, on premature infants was continued at the County Hospital in Los Angeles.

Only premature babies below two thousand grams were employed in this study. Every third child was given methyl testosterone by mouth, every third child testosterone propionate by hypodermic, and every third child given nothing by way of specific treatment. The basic care of all these children was the same.

While all of the data are not yet available and the work continues, there seems to be a significant difference in 1) survival, and 2) weight increase in those children treated by testosterone preparations over those not so treated. The results continue to be promising.

New methods of administration of the hormones have been devised.

47. Equine Pituitary Gonadotropin and Antihormone Formation.

James H. Leathem and A. E. Rakoff. From the Bureau of Biological Research, Rutgers University, New Brunswick, N. J., and the Department of Obstetrics and Gynecology and the Endocrine Division, Jefferson Medical College and Hospital, Philadelphia.

Equine pituitary gonadotropin (Squibb) has been studied to evaluate it in terms of antihormone formation in cases subjected to somewhat extended therapy. Thirteen women suffering from anovulatory sterility or functional menstrual disorders and four hypogonadal males have been studied for antihormone formation. All cases exhibited diminished urinary gonadotropins. In general, the females received 50 units twice weekly during two weeks of each month over a 2–5 month period. The males received 50 units twice weekly for 3–5 months. Antihormones against equine pituitary developed in three women all of whom had been treated for three months and in three males in 3–4 months of therapy. No inhibitory substances existed prior to therapy. Antihormones against equine pituitary were also inhibitory against pregnant mare serum gonadotropin. However, two cases in which the serum lacked anti-equine pituitary substances were able to inhibit pregnant mare serum.

Cases exhibiting a prompt response to equine pituitary were not studied for antihormone formation but of those here presented the cases of functional menstrual disorders exhibited a good response, the males a moderate response, and 3 of 7 cases of anovulatory sterility exhibited improved temperature charts.

Equine pituitary gonadotropin appears to have a distinct stimulating action on the human gonad but also elicits antihormone formation.

48. Studies in Cases of Pituitary Tumors.

K. E. Paschkis, A. Cantarow and A. E. Rakoff. Jefferson Medical College and Hospital, Philadelphia.

Studies are reported on a number of cases of chromophobe adenomas and of parapituitary tumors such as craniopharyngiomas.

The picture of hypopituitarism includes the effects of lack of gonadotropin-, thyrotropin- and adrenocorticotropin secretion. The resulting deficiencies were studied by appropriate methods, in a number of cases both before and after operation.

In insulin tolerance tests "hypoglycemia-irresponsiveness" with prolonged severe hypoglycemia was observed with conspicuous absence of clinical manifestations usually present with severe prolonged hypoglycemia.

Impairment of salt metabolism was present in a number of cases. This indicates that, at least in the human, adrenocorticotropic regulation of the adrenal cortex includes salt-water-metabolism contrary to the claim that the latter function is independent of pituitary regulation.

In one case of pituitary tumor the presence of which was indicated by x-ray of the

sella and by visual field examination, there were hypogonadism (absent gonadotropin excretion, amenorrhoea, atrophic endometrium) and lactating breasts. No other functional abnormalities were present. This patient has not as yet been operated upon, and the nature of the tumor is therefore not known.

49. Carbohydrate Appetite of Normal and Hyperthyroid Rats As Determined by the Taste-Threshold Method.

Curt P. Richter. Psychobiological Laboratory, the Johns Hopkins Hospital, Baltimore, Maryland.

Fifty-four normal and 28 hyperthyroid rats were tested with the taste-threshold method for their appetites for 6 common sugars: maltose, glucose, sucrose, fructose, lactose and galactose. Hyperthyroidism did not change the taste thresholds nor the maximum preference concentrations of these 6 sugars. It did produce a great increase in the appetite for the sugars. The hyperthyroid rats took about twice as much of each of the sugars as did the normal animals. Further, they definitely preferred certain concentrations of the sugars to the stock diet.

Both normal and hyperthyroid rats showed the greatest appetite for the corn sugars, maltose and glucose, the smallest appetite for the milk sugars, lactose and galactose, and intermediate appetites for the cane sugars, sucrose and fructose. The results indicated that the appetites varied directly in proportion to the ability of the rats to assimilate the sugars. It was concluded that hyperthyroidism produces a great increase in the ability of the rats to assimilate carbohydrates.

50. The Effect of Hypothyroidism on Menstruation. W. O. Thompson, P. K. Thompson and E. M. Jeppson, University of Illinois College of Medicine, Chicago, Illnois.

A study of spontaneous myxedema developing in adult life shows that it may produce an increase, a decrease, or a complete absence of menstrual flow. Myxedema developing in adult life as a result of subtotal thyroidectomy often produces an increase in flow but does not seem to produce a decrease. The increase in menstrual bleeding with hypothyroidism may at times be very great, simulating an incomplete abortion and producing a secondary anemia.

Regardless of the type of menstrual disturbance, the administration of thyroid in a suitable dose may correct it. However, when there is a complete absence of menstruation, it may fail to return in some instances following the administration of desiccated thyroid even though the patient is still below the age of the menopause.

The hypothesis that excessive bleeding is the result of primary hypothyroidism while oligomenorrhea and amenorrhea are associated with hypothyroidism secondary to hypopituitarism is not supported by the fact that both types of menstrual irregularity in patients with myxedema may be corrected by the administration of thyroid. The failure of amenorrhea to disappear with thyroid feeding may point to its pituitary origin.

51. Twelve Cases of Metastatic Thyroid Carcinoma Studied with Radioactive Iodine.

S. M. Seidlin, E. Oshry and A. A. Yalow. Montefiore Hospital, New York, N. Y.

After the administration of tracer doses of radioactive iodine to twelve patients with thyroid carcinoma, the metastases were studied for uptake of the isotope by means of the Geiger-Mueller counter. Six cases were positive (metastases showed uptake of radioiodine), three were negative and three questionable. The radio-autographs were positive in seven, negative in the three and questionable in two. The possible correlation of histological structure of the tumors and radioiodine uptake was attempted. The effect of pre-

treatment with thyrotropic hormone and thiouracil on radioiodine uptake by the metastases was also studied. Radioiodine concentration in the blood and urinary excretions were carried out in all cases. All "positive" cases received or are receiving therapeutic doses of radioactive iodine.

52. GOITER ON AN IODINE-FREE DIET GROWN BY HYDROPONICS, AND EXCLUDING ANY GOITER NOXA.

J. F. McClendon and Wm. C. Foster. Hahnemann Medical College, Philadelphia.

In order to produce an iodine-free diet and exclude a goiter noxa we grew a diet by hydroponics in a disinfected greenhouse with disinfected water and chemicals in a goiter-free region. Air was pumped through a carbon filter. Six litter-mate rats from a colony that had been goiter-free for 6 years were put at weaning on the diet of 40 per cent sunflower seed, 2.8 per cent soy beans, 40 per cent sucrose, 0.8 per cent NaCl and 16.4 per cent corn oil. Three of the rats were given water redistilled from alkali to drink and at the end of 73 days had goiters weighing 39, 42 and 41 mg. per 100 Gm. body weight. The other 3 rats were given water containing 10 parts per million of iodine and had normal thyroids weighing 10 mg. per 100 Gm. body weight. Since the rat cages were enclosed in a cellophane covered frame and no goitrous animals or humans had access to the we believe that so called goiter noxa is excluded. The goiters were 4 times as large as normal thyroids and twice as large as goiters in rats from a goitrous colony fed in a goiter region on a very low iodine diet.

53. MITOTIC ACTIVITY AND WOUND HEALING IN THE CORNEAL EPITHELIUM OF RATS TREATED WITH THIOURACIL.

Walter Fleischmann and Alfred Breckler. Clinical Physiology Section, Medical Division, Edgewood Arsenal, Maryland, and Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland.

The corneal epithelium of the rat has been shown to be a suitable test object for mitotic and wound healing activity. (Buschke, Friedenwald and Fleischmann, *Bull. Johns Hopkins Hosp. 73:* 143, 1943; Friedenwald and Buschke, *J. Cell. and Comp. Physiol. 23:* 95, 1944.) We have compared mitotic counts in flat preparations of corneae of rats treated with thiouracil with those of litter-mate controls. A number of animals were given 5 mg. of colchicine per kg. of body weight 4 hours before killing them, others were killed without previous treatment with colchicine. The number of mitoses as estimated from the colchicine experiments was significantly reduced in the rats treated with thiouracil. In the experiments without colchicine the counts were not reduced in the rats treated with thiouracil. This indicates that not only the onset of mitosis, but the duration of the mitotic cycle is slowed down in thiouracil treated rats. Superficial wounds of the cornea heal in the same time in hypothyroid rats as in normal controls.

Papers read by title

54. CLINICAL MANIFESTATIONS IN FORTY CASES OF MYXEDEMA.

David Schwimmer, Mildred Vogel, and Thomas H. McGavack. From the New York Medical College, Metropolitan Hospital Research Unit.

Data are presented on forty cases of myxedema seen during the past seven years in both hospital and office practice. Observation has varied from 12 hour antemortem to over five years.

Stress is laid on the presenting clinical manifestations, chiefly as they concern proper diagnosis. It is felt that far too often the diagnosis of myxedema is missed primarily because it is not entertained as a possibility. An important contributing factor in such

failures of recognition of the disease is that the diagnosis generally is based on the classical findings of obesity, dry skin, coarse hair, hoarse voice, apathy, etc.

While it is true that these classical manifestations are unmistakable, such standard findings may be absent. In 20–30 per cent the myxedematous status was masked by symptomatology of cardiac difficulties. "Nervousness," rather than apathy and complacence, was prominent in over 60 per cent.

The cases presented are divided into four groups:

I. Those with classical symptomatology.
II. Those with predominantly cardiac manifestations.
  a. cardiac symptoms without congestive failure.
  b. cardiac symptoms with congestive failure.
  c. cases of coronary occlusion.
III. Those with atypical symptomatology.
IV. Those without symptoms.

Emphasis is placed on the fact that cardiac failure may raise the basal metabolic rate to normal or above; also, that the serum cholesterol levels may be unexpectedly normal, especially with chronic passive congestion of the liver incident to right heart failure.

55. Thiouracil in the Treatment of Hyperthyroidism Complicating Pregnancy and Its Effects on the Fetus.

M. James Whitelaw. From the Department of Obstetrics and Gynecology, Southwestern Medical College.

The relative infrequency of hyperthyroidism as a complication of pregnancy is discussed giving the statistical figures from both European and American sources. A severe hyperthyroid pregnant white female in the 26th week of gestation was treated with thiouracil up to and through the puerperium. She presented the classical clinical as well as laboratory findings characteristic of Graves disease. Her BMR was +65. Under thiouracil therapy .4 gram per day given in divided doses plus general supportive measures, she was symptom free at the time of her delivery. Her BMR had fallen within normal range as had her pulse, blood chemistry and circulation time. An anencephalic monster was delivered which died 6 hours postpartum. Autopsy revealed a thyroid gland that appeared both microscopically and histologically normal. The weight and iodine content of the thyroid were both well within normal limits.

56. The Permanency of Alloxan Diabetes and the Structure of the Pancreatic Islets Following Certain Experimental Procedures.

Ralph G. Janes, Department of Anatomy, College of Medicine, State University of Iowa, Iowa City.

When alloxan is given to the rat either subcutaneously, intraperitoneally, or intrasplenically, there is considerable variation in the severity of the resulting diabetes. In mildly diabetic animals (blood sugar up to 250 mg. % and urine volume below 100 cc. daily) the diabetic symptoms usually disappear in 4–6 weeks. In severely diabetic rats (blood sugar levels up to 900 mg. % and urine volumes up to 300 cc. daily) the diabetes remains severe until death. Although it is not always possible to correlate the severity of the diabetes with the amount of islet damage, in general the more severe the diabetes, the more extensive is the islet destruction. When suitable quantities of alloxan are administered the islets lose their brilliant staining qualities, cell boundaries become indistinct, and many of the Beta cells exhibit necrotic changes. Furthermore, islet cell nuclei become more abundant at the periphery, resulting either from shrinkage of the cytoplasm of certain islet cells or perhaps from cell division. In 3–4 weeks following the

injection of alloxan, some of the Beta cells which are not destroyed regain their staining qualities and connective tissue replaces those which are destroyed. In an attempt to modify further the islets following this period, the animals were subjected to several procedures which have been shown to alter carbohydrate metabolism, namely, diets high in niacin, diets with large amounts of thiamine, high fat diets and thiamine deficient diets. No further alteration in the islets has been noted following these procedures.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor; D. A. McGINTY, *Collaborators;* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.

PANCREAS

EDMONDSON, H. A., HELEN E. MARTIN, AND N. EVANS. Necrosis of renal papillae and acute pyelonephritis in diabetes mellitus. *Arch. Int. Med. 79:* 148 (1947).

Acute necrosis of the renal papillae was observed in 29 of 859 diabetic subjects in a series of 32,000 necropsies. Papillary necrosis is more common in women and is exceedingly rare in patients under 40 years of age as contrasted with pyelonephritis without necrosis in diabetic patients, among whom men predominate and occurrence under 40 is not unusual. The disease is highly fatal; only once was healing observed. It is most often part of acute pyelonephritis, which may be secondary to ascending infection of the urinary tract or to pyogenic foci elsewhere in the diabetic subject. Colibacilli and Staphylococcus aureus are the organisms most frequently isolated from acute pyelonephritis. The latter disease may be secondary to sepsis, which is an important cause of pyelonephritis in diabetic patients. Tuberculosis and actinomycosis were each noted once as the cause of papillary necrosis. The diabetic state, renal vascular disease (including Kimmelstiel-Wilson disease) and poor blood supply of the papillae are apparently contributing factors in the pathogenesis. In the same necropsy series, papillary necrosis was noted in 21 of 1,023 patients with pyelonephritis who were not diabetic; in 20 it occurred as a complication of urinary obstruction, which was most often due to disease of the prostate gland. Criteria for the diagnosis of papillary necrosis in diabetic patients cannot be rigidly defined but should include hematuria, renal colic, unexplained coma and sudden increase in severity of symptoms of known pyelonephritis. Retrograde pyelograms are usually diagnostic. Treatment should be directed toward preventing infection by early use of chemotherapy. After the onset of pyelonephritis, specific chemotherapeutic agents should be used in adequate amounts, as some patients may be saved.—(Authors' Summary and Conclusions)—*I.B.*

WHITE, PRISCILLA. Pregnancy complicating diabetes. *Pennsylvania M. J. 50:* 705 (1947).

When pregnancy complicates diabetes, five abnormalities may be revealed. These are maternal, obstetrical, chemical, fetal and placental in nature. In a series of 300 cases, the maternal abnormalities were vascular disease and hypo-ovarianism. The obstetrical abnormalities were an irritable uterus including early rupture of membranes with

premature loss of amniotic fluid but postponement of delivery for months, spontaneous abortion (25 per cent) and pre-eclampsia (40 per cent). Breech presentation was found in 33 per cent. Uterine inertia and shoulder dystocia were common. The chemical abnormalities were three—the low renal threshold for sugar, the disturbance of water balance, and the imbalance of the sex hormones of pregnancy. The fetal abnormalities included physical, chemical and pathological changes. Eighty per cent of the infants were large, due to obesity, to edema or to splanchnomegaly. Jaundice was almost a universal occurrence in infants of diabetic mothers. Atelectasis varied with prematurity The chemical characteristic of these infants was instability of the blood sugar. The pathological abnormalities included a syndrome not unlike that of erythroblastosis without anemia and occurred in Rh-positive mothers. There was advanced bone and gonad development. Placental abnormalities were two: extreme hypertrophy of the placenta, or a placenta that was abnormally small. The most important harmful factor appeared to be the disturbance of the sex hormones. Thus, when the hormonal balance was normal, as it was in 66 of the series, the maternal survival was 100 percent, the fetal survival 97 percent; the incidence of pre-eclampsia was 2 percent and of premature deliveries, zero. Only when the entire endocrine and vascular problem of diabetes is solved will the results in obstetrical diabetes be exactly comparable to those of nondiabetic obstetrical experience.—*I.B.*

ROOT, H. F., E. STOTZ, AND T. M. CARPENTER. The respiratory quotient and blood pyruvate and lactate responses after oral ingestion of glucose and fructose in diabetes mellitus with and without insulin. *Am. J. M. Sc. 211:* 189 (1946).

The respiratory quotient (R.Q.), the blood sugar, and the pyruvate (PA) and lactate (LA) levels of the blood were determined in diabetic patients before and after the oral ingestion of 50 Gm. of glucose or fructose. In a group of 26 patients who had been without insulin for varying lengths of time preceding the tests, slight rises in R.Q. after ingestion of glucose were not generally accompanied by rises in PA and LA, but when the rise in R.Q. was 0.05 or over, there was usually a rise in either PA or LA or both. With one exception, when there was no rise in R.Q. there was no significant change in the acid level of the blood. In a group of 20 patients, when insulin was given immediately preceding or immediately following the ingestion of glucose, the majority showed rises in the R.Q. and acid levels of the blood, and these changes were in some patients larger than would occur with the majority of normal subjects. Insulin resistant cases required larger amounts of insulin to produce a rise in R.Q. after administration of glucose. The rises in R.Q. could have been due only partially to the displacement of carbon dioxide from the blood by the organic acids. The ingestion of 50 Gm. of fructose by 15 patients produced a rise in R.Q. in 10 of them, and in all of them the PA and LA levels were increased even when no rise in R.Q. took place. In only 2 patients was the ingestion of fructose accompanied by simultaneous injection of insulin. The rises in R.Q. and organic acid levels of the blood were, in general, larger than after the same amount of glucose. The intermediary metabolism of fructose appears to be different from that of glucose in diabetic patients as well as in normal persons. The authors conclude that these studies contribute to the "under-oxidation" theory of diabetes and show that the action of insulin is to promote the formation of PA, an intermediate which leads to oxidation. The increase in oxidation is very definitely shown in the greater rises in R.Q. when insulin is given with the sugars.—*E.C.R., Jr.*

WOLMAN, I. J. Melituria in healthy American men with special reference to transitory glycosuria. *Am. J. M. Sc. 212:* 159 (1946).

The nature and incidence of melituria as encountered in 77,293 consecutive healthy males at the time of their arrival at the Maritime Service Training Station, Sheepshead Bay, Brooklyn, has been surveyed by the author. Of these men, 225 (0.29%) were found to have transitory benign melituria; 19 (0.02%), low renal threshold; 7 (0.01%), persistent renal glycosuria; 52 (0.07%) were undiagnosed; and 21 (0.03%) had diabetes mellitus which had escaped detection in the enrolling offices. No instances of congenital non-dextrosic melituria were recognized. Not included in this tabulation are some additional cases of diabetes which came to light during the course of training, men whose urine examinations had been negative on arrival. The analysis of the patients with melituria on admission revealed: 1) the transitory form tended to become more frequent with advance in age; 2) the concentration of the sugar in the urine proved of little aid as a guide to diagnosis; and 3) the mechanism which provoked the transitory form in some subjects on the first day of training was far from clear. The author believes that emotional influences, fatigue, inflexibility of metabolic adjustments, and poor "carbohydrate saturation" must have played roles of inconstant and differing importance. The blood sugar was not elevated in many of the subjects at the hour when their urines were positive for sugar.—*E.C.R., Jr.*

GENERAL

BAYLOR, N. Tables for predicting height from the skeletal age and present height. *J. Pediat. 28:* 49 (1946).

The author has developed 8 tables for estimating the probable adult height of children whose growth is still incomplete. These tables are based on data assembled for children between the age of 7 years and maturity of Massachusetts (Harvard Growth Study) and California (University of California Institute of Child Welfare). In order to allow for differences in sex and in velocities of maturation, tables have been prepared for each age group of each sex. In developing the tables, it was found that for the average child the percentage of his own ultimate adult stature at any point correlated more closely with his skeletal age by Todd standards than with his chronological age. However, in certain children under 12 years where marked acceleration or retardation existed the correlation was better with the chronological than with the skeletal age. In use, one selects the correct table for the child's sex, skeletal age (determined from the x-ray of the ossification centers of the hand or other bones), and degree of acceleration or retardation, and reads the prediction of ultimate height directly from the table. A special table has been prepared to give more accurate predictions for children under 13 years whose skeletal and chronological ages differ by more than one year. The accuracy of the predictions in general is better than one inch except for isolated cases in the younger age group. The tables are most accurate and of greatest value during the period of adolescent growth spurts (after 10 years for girls and 12 years for boys). The predictions are not valid in cases in which the regulators of growth are not functioning normally.—*E.C.R., Jr.*

SCHNEIDER, C. L. The active principle of placental toxin: thromboplastin; its inactivator in blood: antithromboplastin. *Am. J. Physiol. 149* (1): 123–129 (1947).

Extracts of rabbit lung, brain, kidney, liver, skeletal muscle, pseudopregnant rabbit

uterus and human term placenta were made. The toxin activity was measured with the mouse assay method previously reported by the author. The mouse unit of toxin is defined as the minimum lethal dose for mice of 20 grams' body weight. The results confirmed the work of the author and others that tissue extracts, especially placental extracts, possess a toxin which has been regarded as a causative agent in toxemia of pregnancy. It was concluded that this toxin is thromboplastin, that its lethal effect depends on intravascular clotting and that antithromboplastin is the inactivator of the toxin. It is suggested, but not concluded, that thromboplastin may be the cause of toxemia of pregnancy.—*F.N.A.*

REYNOLDS, S. R. M. The relation of hydrostatic conditions in the uterus to the size and shape of the conceptus during pregnancy: a concept of uterine accommodation. *Anat. Rec. 95:* 283–296 (1946).

Accommodation of the rabbit uterus to the conceptus is divided into three phases: preparation by cellular proliferation, enlargement by hypertrophy and uterine stretching with enlargement of the fetus. The period of enlargement is characterized by spheroidal conceptuses. The fetus then elongates as uterine growth ceases at which time stretching of the uterine wall occurs. Since tension in a circular direction in a spheroid is less than in a longitudinal direction, accommodation to the conceptus during the period of stretching occurs by elongation because resistance to lengthening is one-half that to an increase in diameter. Maximum uterine growth is directly related to tension on the uterus exerted by the spheroidal conceptus whereas circulation of maternal blood is inversely related to this tension. Fetal death occurs most frequently at the end of the period of uterine enlargement and the rate of fetal growth is greatest during the period of stretching.—*B.L.B.*